Human Skeletal Muscle Mitochondrial Adaptations Following Resistance Exercise Training

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ABSTRACT

It is universally accepted that resistance training promotes increases in muscle strength and hypertrophy in younger and older populations. Although less investigated, studies largely suggest resistance training results in lower skeletal muscle mitochondrial volume; a phenomenon which has been described as a "dilution of the mitochondrial volume" via resistance training. While this phenomenon is poorly understood, it is likely a result of muscle fiber hypertrophy outpacing mitochondrial biogenesis. Critically, there is no evidence to suggest resistance training promotes a net loss in mitochondria. Further, given the numerous reports suggesting resistance training does not decrease and may even increase VO_2max in previously untrained individuals, it is plausible certain aspects of mitochondrial function may be enhanced with resistance training, and this area warrants further research consideration. Finally, there are emerging data suggesting resistance training may affect mitochondrial dynamics. The current review will provide an in-depth discussion of these topics and posit future research directions which can further our understanding of how resistance training may affect skeletal muscle mitochondrial physiology.

Introduction

Mitochondria are cellular organelles that produce most of the ATP during aerobic conditions [1]. Mitochondrial proteins are encoded by both mitochondrial DNA and nuclear DNA. The integration of both protein pools provides a unique environment where adaptations to both mitochondrial DNA and nuclear DNA must occur for optimal functioning of the mitochondria. Due to the importance of mitochondria in bioenergetics, researchers have sought to examine mitochondrial differences between healthy and diseased individuals.

Investigations on how mitochondria adapt are plentiful, with the first publications documenting the organelle in the 1840s [2]. In the field of exercise physiology, the study of skeletal muscle mitochondrial adaptations to endurance training was largely spurred by Dr. John Holloszy's 1967 publication demonstrating that mitochondrial enzyme activities in the hind limb muscles of rats were two-fold higher in animals that treadmill-trained for 12 weeks versus age-matched sedentary controls [3]. Other studies have since reported that an increase in aerobic capacity due to training are in part due to improvements in mitochondrial biogenesis and function [3–7]; however the exact signaling cascades that allow for such responses are still being investigated [8]. These topics are not the focus of the current review, and readers interested in this information are directed to other excellent reviews [9–11].

Well-known resistance training adaptations include increases in strength and muscle hypertrophy. Several reviews on this topic have been written, and we encourage readers to refer to these papers for more nuanced discussion [12–14]. In novice trainees, chronic resistance training results in an increase in strength followed by an increase in muscle size [15]. Rapid strength adaptations have been attributed to neural adaptations (e. g., increased motor unit recruitment and synchronization, decreased co-contraction of antagonist muscles, increased neural drive from the central nervous system, and increased motor unit hypertrophy) [14, 16, 17]. Strength adaptations are associated with lifting intensities such that higher training loads (e. g., repetitions at 85–90 %

one repetition maximum) will result in a greater strength adaptation compared to lower loads (e. g., repetitions at 55–65 % one repetition maximum) [15, 18]. There are a plethora of molecular events that facilitate skeletal muscle hypertrophy (e. g., increases in mammalian target of rapamycin complex 1 signaling leading to an upregulation in protein synthesis, increases in ribosome biogenesis, and myonuclear accretion), and readers are directed to other reviews for a discussion of these signaling events [19–21].

Studies have found equivocal results regarding mitochondrial adaptations with resistance training, with some reporting increases or no changes in markers of mitochondrial biogenesis or oxidative capacity following resistance exercise training [15, 18, 22, 23]. Resistance training has also been of great interest in an elderly population given that the ability to maintain or improve strength results in a better quality of life and a reduction in frailty-related outcomes [24–26]. Interestingly, older individuals have been reported to experience an increase in mitochondrial biogenesis and oxidative capacity following periods of resistance training [27–29]. This may suggest that mitochondrial adaptations with resistance training occur in a population-specific manner. Notwithstanding, studies investigating mitochondrial adaptations with resistance training have heavily focused on various enzyme activities, and few studies have directly investigated mitochondrial respiration rates [23, 28–35].

The primary purpose of this review is to provide an overview of what is currently known regarding mitochondrial adaptations following resistance training (summarized in ▶ **Table 1**). Additionally, there will be a brief discussion of how resistance training in elderly individuals is beneficial for combating sarcopenia, and we discuss how resistance training may provide mitochondrial benefits that are not consistently observed in younger, healthier populations. Lastly, we will briefly discuss investigative avenues that could be pursued to better understand how resistance training affects mitochondrial adaptations. The current review meets the ethical standards of the International Journal of Sports Medicine as discussed in Harriss et al. [36].

Mitochondrial adaptations to resistance training in younger individuals

Measuring mitochondrial content (or volume) in human skeletal muscle can be technically challenging for a variety of reasons. First, muscle biopsies are required, which itself presents a significant barrier for many exercise physiology laboratories. Examining the relative space occupied by the mitochondria using high-resolution transmission electron microscopy is the gold standard in determining mitochondrial volume [37]. However, transmission electron microscopy methodologies are laborious, and the equipment needed for these analyses is not widely accessible. Other surrogate measures in biopsy specimens have been used to determine mitochondrial volume, and a study by Larsen et al. [37] determined that citrate synthase activity as well as complex I-V protein content and activity were highly correlated with mitochondrial volume as assessed using transmission electron microscopy imaging.

Many studies have examined mitochondrial adaptations that occur in response to endurance training [38–41]. During endurance training, mitochondrial biogenesis facilitates mitochondrial

growth through numerous molecular interactions. There is ample evidence to suggest that the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) protein is largely involved with mitochondrial biogenesis [42]. For instance, PGC-1α works in concert with other proteins, such as peroxisome proliferator-activated receptor beta (PPARβ), to facilitate interactions with other nuclear transcription factors to up- or down-regulate mitochondrial biogenesis [8, 43]. PGC-1α has been shown to regulate the transcriptional activity of the peroxisome proliferator-activated receptor gamma (PPARγ) nuclear receptor that in turn up-regulates the expression of electron transport chain genes [44]. PGC-1α binds to and activates the nuclear respiratory factor-1 (NRF-1) transcription factor in muscle cells, thereby upregulating genes that facilitate mitochondrial DNA replication [45]. These findings are bolstered by numerous reports suggesting endurance training promotes mitochondrial biogenesis through the induction of PGC-1α expression following a bout of training [46–49]. The relationship between mitochondrial volume density and relative VO_2max has been suggested for many years [8, 50]. Likewise, correlations have been observed between skeletal muscle oxidative capacity and VO_2max as well as mitochondrial volume density and VO_2max following conventional endurance and intermittent training [10, 51, 52]. Thus, mitochondrial adaptations to endurance training are seemingly critical in facilitating increases in aerobic exercise performance.

Although mitochondrial biogenesis has been well documented in response to endurance training, the mitochondrial adaptations that occur in response to resistance training are not as clear. In the early 1980s, MacDougall et al. [53] characterized the skeletal muscle of healthy male participants who underwent resistance training for six months. These researchers reported that training significantly increased cross-sectional area for both type I and type II fibers. Electron microscopy additionally revealed that mitochondrial volume relative to myofibrillar volume significantly decreased with training, whereas cytoplasmic volume significantly increased. These results agreed with earlier observations by the same laboratory [34], and the researchers stated that "…resistance training leads to a dilution of the mitochondrial volume". A subsequent study demonstrated similar findings in 8 male subjects who resistance-trained for six weeks [15]; specifically, increases in strength and vastus lateralis muscle cross-sectional area were observed, whereas a significant decrease in mitochondrial volume as measured by transmission electron microscopy occurred. **Figure 1** depicts a simplistic schematic of these observations.

The notion of resistance training-induced mitochondrial dilution has also been supported by several studies that have assessed the activities of various mitochondrial enzymes in muscle homogenates. For instance, 6 months of resistance training has been shown to decrease the enzymatic activity of citrate synthase [54], which as stated above, is strongly correlated with mitochondrial volume. Additionally, 12 weeks of resistance training results in significant increases in cross-sectional area of both fiber types as well as significant decreases in protein content of the mitochondrial succinate dehydrogenase enzyme [30, 31]. Our research group recently reported that high hypertrophic responders to 12 weeks of resistance training possessed higher citrate synthase activity com-

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▶ **Table 1** Summary of studies that investigated the effect of resistance training on mitochondrial function.

Study	Sample Size	Training Intervention	Mitochondrial Measurement Technique	Mitochondrial Protein Markers/ Activities	Mitochondrial Respiration	Mitochondrial Volume	Muscle Fiber Size	Conclusion
[23]	11 Young Males	RT 3x/week for 12 weeks @ 60–80 % 1RM	Muscle biopsies (VL) to measure mitochondrial capacity via permeabilized fibers	↑ CI Protein Content ↑ COX4I1 mRNA ↑ NAMPT mRNA	↑ CI substrate respiration ↑ CI + CII substrate respiration ↓ CII substrate control ratio	↔ CS Activity	↑	Resistance training increases respiratory capacity mainly through CI adaptations
[28]	15 Old Males & 15 Old Women	RT 3x/week for 14 weeks @ 50 % 1RM to 80 % 1RM	Muscle biopsies (VL) to measure enzyme activities	↑ CIV Activity ↑ CIV/CI + III Activity	NA	↔ CS Activity	NA	Resistance training increases activity of ETC enzymes
[29]	12 Old Males	RT 3x/week for 12 weeks @ 50 % 1RM to 80 % 1RM	Muscle biopsies (VL) to measure enzyme activities	↑ Catalase Activity ↑ SOD1 Activity	NA	↔ CS Activity	↑	Resistance training increases activity of antioxidant enzymes
[30]	15 Young Males & Females	RT 3x/week for 12 weeks @ 2–84 % 1RM	Muscle biopsies (VL) to measure enzyme activity	↓ SDH Activity	NA	NA	↑	Resistance training increases muscle hypertrophy while decreasing mitochondrial enzyme activity
[31]	6 Young Males	RT 3x/week for 12 weeks @ 3 sets of 6–8 repetitions to failure	Muscle biopsies (VL) to measure enzyme activity	↔ SDH Activity	NA	NA	↑	Resistance training increases muscle hypertrophy while causing no change in mitochondrial enzyme activity
[32]	25 Young Males	RT 3x/week for 12 weeks @ 50–108 % 1RM	Muscle biopsies (VL) to measure mitochondrial enzyme content and activities	↔ PGC-1α protein content ↔ OXPHOS protein content	NA	↓ CS Activity	↑	Resistance training increases muscle hypertrophy and decreases mitochondrial protein content and volume
[33]	22 Young Males	All individuals performed 1 bout of continuous exercise and 1 bout of knee extensions for an acute RT	Muscle biopsies (VL) to measure oxidative respiration via permeabilized fibers	NA	↑ State 3 respiration ↔ Leak respiration ↑ Respiratory control ratio	↔ CS activity	↑ in RT subjects	Resistance training individuals had a higher oxidative respiration despite having a lower VO₂ peak when normalized to whole body muscle mass
[34]	6 Young Males	RT 3x/week for 6 months @ 3–5 sets of 8–10 reps to failure	Muscle biopsies (TB) to measure V$_{mito}$ via electron microscopy	NA	NA	↓ V$_{mito}$	↑	Resistance training causes mitochondrial dilution
[53]	12 Young Males	5 individuals underwent RT 3x/week for 6 months. 7 individuals were elite bodybuilders	Muscle biopsies (TB) to measure V$_{mito}$ via electron microscopy	NA	NA	↓ V$_{mito}$	↑	Resistance training causes mitochondrial dilution

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▶ **Table 1** Continued...

Study	Sample Size	Training Intervention	Mitochondrial Measurement Technique	Mitochondrial Protein Markers/ Activities	Mitochondrial Respiration	Mitochondrial Volume	Muscle Fiber Size	Conclusion
[54]	21 Young Males	RT 3x/week for 6 months	Muscle biopsies (VL) to measure enzyme activities	↓ Hexokinase ↓ Myofibrillar ATPase ↓ Phosphofruc-tokinase ↔ Lactate Dehydrogenase ↓ Myokinase ↓ Creatine Kinase	NA	↓ CS Activity	↑	Resistance training results in decreases in both glycolytic and oxidative enzyme actives
[55]	30 Young Males	RT 3x/week for 6 weeks @ 60% 1RM	Muscle biopsies (VL) to measure enzyme activities	NA	NA	↓ CS Activity	↑	Resistance training resulted in mitochondrial dilution
[56]	26 Young Males	RT 3x/week for 12 weeks @ 4–5 sets of 12 reps to failure concentric and/ or eccentric movements	Muscle biopsies (VL) to measure enzyme activity	↔ Phosphofruc-tokinase ↔ Hexokinase ↔ Lactate Dehydrogenase ↔ Myokinase ↔ Mg^{2+} ATPase	NA	↔ CS Activity	NA	Resistance training results in no changes in glycolytic or oxidative enzyme activity
[57]	24 Young Females	RT 2x/week for 20 weeks @ 40 to 85% 1RM	Muscle biopsies (VL) to measure enzyme activity	↔ Creatine Kinase ↔ Phosphofruc-tokinase ↔ GAPDH ↑ Cytochrome Oxidase ↔ HADH ↑ Hexokinase	NA	↑ Absolute V_{mito} ↔ Percent V_{mito} ↔ CS Activity	↑	Resistance training decreases type IIB fibers along with an increase in important oxidative phosphorylation enzyme activity
[58]	12 Young Males	RT 5x/week for 12 weeks @ repetitions to failure, starting at 10–12 week 1 and going to 5–6 repetitions	Muscle biopsies (VL) to measure enzyme activity	↑ β-HAD ↑ Hexokinase ↔ Phosphofruc-tokinase	NA	↑ CS Activity	↑	Resistance training increases glycolytic and oxidative enzyme activities
[65]	8 Young Males & Females	One-legged cycle training in normoxic or hypoxic environment for 4 weeks @ 65% maximal power output	Muscle biopsies (VL) to measure oxidative respiration via permeabilized fibers and enzyme activities	↔ COX activity	↔ State 3 respiration ↔ State 4 respiration ↔ Respiratory control ratio ↔ P/O ratio	↑ CS activity with normoxia	NA	Adaptations observed in normoxia were abolished with hypoxia.
[67]	21 Young Men	RT 3x/week for 10 weeks @ 30% 1RM or 80% 1RM	Muscle biopsies (VL) to measure mitochondrial protein content	↑ COX IV ↔ Cytochrome c ↑ OPA1 with 30% 1RM ↑ Fis1 with 30% 1RM ↑ Drp1 with 30% 1RM ↑ SOD 1	NA	NA	↑	Resistance training at a lower load (30% 1RM) resulted in similar hypertrophy increases with additional increases in mitochondrial dynamic markers

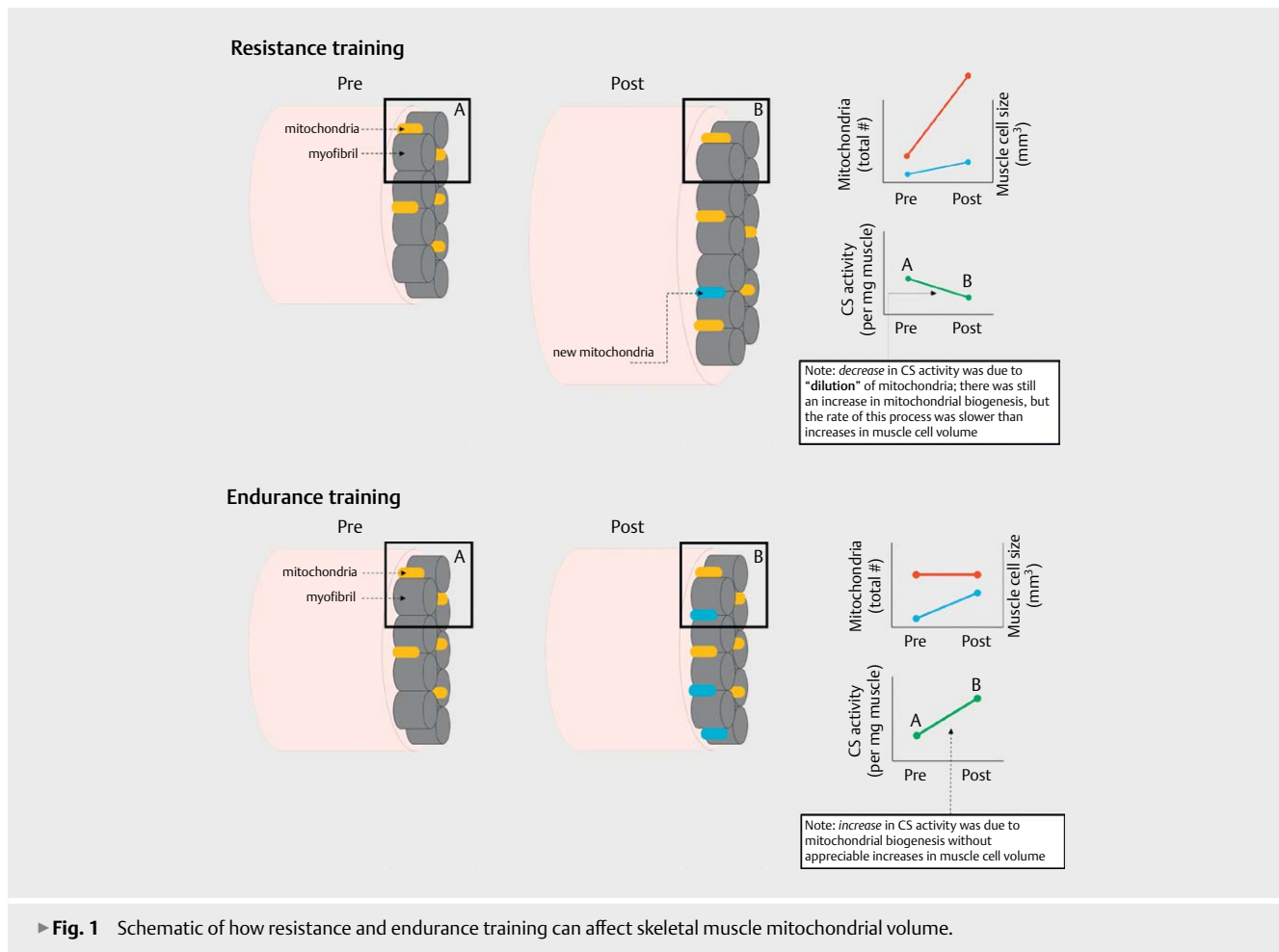| Study	Sample Size	Training Intervention	Mitochondrial Measurement Technique	Mitochondrial Protein Markers/ Activities	Mitochondrial Respiration	Mitochondrial Volume	Muscle Fiber Size	Conclusion
[84]	10 Old Males	RT 3x/week for 12 weeks @ 80% 1RM	Muscle biopsies (VL) to measure oxidative respiration via permeabilized fibers and enzyme activities	↔ CI protein content ↔ CII protein content ↔ CIII protein content ↔ CIV protein content ↑ ADP sensitivity	↑ State 3 respiration ↔ State 4 respiration ↔ RCR	NA	↔	Resistance training improved ADP sensitivity in older individuals with no change to the electron leak to H_2O_2
[85]	27 Old Males & Females 45 Young Males & Females	RT 2x/week for 12 weeks @ 4 sets of 8–12 repetitions	Muscle biopsies (VL) to measure oxidative respiration via differential centrifugation	↑ 6 Mitochondrial specific mRNA ↑ Mitochondrial fractional synthesis rate in older individuals	↔ State 3 CI + II substrates	NA	NA	Resistance training resulted in enhanced proteins for the mitochondria, potentially through enhancing translational capacity
[86]	19 Old Males	RT 3x/week for 12 weeks @ 8–12 repetitions to failure	Muscle biopsies (VL) to measure oxidative respiration via differential centrifugation and enzyme activity	↓ PGC-1α mRNA content ↑ β-HAD activity ↔ ROS production	↔ Pyruvate oxidation ↔ Fatty acid oxidation	↔ CS Activity	↔	Resistance training at a low volume does not change skeletal muscle oxidative capacity

ADP (adenine diphosphatase), β-HAD(3-hydroxyacyl-CoA dehydrogenase), CI (complex I), CII (complex II), CII (complex III), CIV (complex IV), COX4l1 (cytochrome c oxidase subunit 4 isoform 1), CS (citrate synthase), Drp1(dynamin related protein 1), ETC (electron transport chain), Fis1(mitochondrial fission 1 protein), GAPDH (glyceraldehyde 3-phosphate dehydrogenase), H_2O_2 (hydrogen peroxide), HADH (hydroxyacyl-coenzyme A dehydrogenase), NAMPT (nicotinamide phosphoribosyltransferase), OPA1 (OPA1 mitochondrial dynamin like GTPase), OXPHOS (oxidative phosphorylation), PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), RCR (respiratory control ratio), RM (repetition maximum), ROS (reactive oxygen species), RT (resistance training), SDH (succinate dehydrogenase), SOD (superoxide dismutase), TB (triceps brachii), VL (vastus lateralis), Vmito (volume of mitochondria).

pared to low responders [32]. However, citrate synthase activity decreased in both cohorts with resistance training. Additionally, we recently reported six weeks of high-volume resistance training significantly decreased muscle citrate synthase activity during weeks 3 (mid-testing) and 6 (post-testing) in lieu of cytoplasmic expansion within muscle fibers [55]. Interestingly, the mitochondrial dilution response to training does not seem to be specific to muscle fiber type. Green et al. [31] reported that following 12 weeks of resistance training, there was an increase in the cross-sectional area of all fiber types in the quadriceps muscle, but no changes were observed in succinate dehydrogenase (SDH) activity in any fiber type. Similar findings (i. e., increases in cross-sectional area with no change in overall SDH activity) have also been reported elsewhere [30].

Not all studies report that mitochondrial volume decreases with resistance training. For instance, one study examined skeletal muscle adaptations in 20 males who completed a resistance training protocol for 12 weeks [56]. Enzyme activities of citrate synthase as well as phosphofructokinase, hexokinase, lactate dehydrogenase, myokinase, and Mg^{+2}-stimulated ATPase were measured. Researchers observed no statistically significant differences in any of these

enzyme activities following resistance training, which suggests that neither mitochondrial volume density nor cytosolic enzymes were diluted with training. A maintenance of mitochondrial volume in females has also been observed following 20 weeks of resistance training [57]. Additionally, these authors observed a significant increase in cytochrome c oxidative (complex IV) activity with no significant changes in citrate synthase activity.

In contrast to the several studies above reporting a dilution effect with mitochondria in response to resistance training, findings are inconsistent regarding whether training alters the intracellular concentrations of glycolytic enzymes. Wang et al. [57] observed a significant increase in vastus lateralis hexokinase activity following 18 weeks of resistance training. Similarly, Tang et al. [58] observed a significant increase in vastus lateralis hexokinase activity after 12 weeks of resistance training, but phosphofructokinase activity was not altered. As discussed above, Tesch at al. [56] did not observe significant changes in either hexokinase or phosphofructokinase activity in vastus lateralis after 12 weeks of resistance training. Another paper states that the relative abundance of numerous glycolytic enzymes increased in the vastus lateralis in response to six weeks of high-volume resistance training [55]. These data collec-

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▶ Fig. 1 Schematic of how resistance and endurance training can affect skeletal muscle mitochondrial volume.

tively suggest that although mitochondrial dilution may occur with resistance training, there may be an increase or no change in glycolytic enzyme concentrations. Alternatively stated, these data largely suggest that a dilution of mitochondria occur with resistance training, whereas other metabolic enzymes in the sarcoplasm are maintained.

Fewer studies have investigated the effects of resistance training on mitochondrial function and oxidative potential. One study involved 12 weeks of resistance training, and oxidative function in permeabilized fibers was assessed [35]. The authors reported that resistance training resulted in a nonsignificant increase in citrate synthase activity (measured from muscle homogenates), a significant increase in maximal respiration from complex I stimulated by ADP when normalized to maximal uncoupled respiration, and a significant increase in complex I protein content. These results suggest that resistance training resulted in improved functional changes mainly driven through complex I. Interestingly, the same researchers noted a decrease in the ability of the skeletal muscle to produce ATP through electron flow via complex II despite an increase in total maximal respiration.

Salvadego et al. [59] measured oxidative function in 11 males classified as resistance trained and 11 males who were physically active but did not actively participate in resistance training. A muscle biopsy was taken from the vastus lateralis, and mitochondrial function was measured in permeabilized fibers. In agreement with the previous investigation cited above [35], the resistance-trained individuals presented higher state 3 respiration and respiratory control ratio (RCR) values. Notably, state 3 respiration is the measure of maximal ATP production and RCR is the ratio between state 3 respiration and state 4 respiration (basal ATP production), a functional measure of overall mitochondrial function [60]. Additionally, these researchers observed no significant differences in citrate synthase activity between the resistance-trained individuals and control subjects. Interestingly, Salvadego and colleagues hypothesized that O_2 delivery may be impaired during muscle hypertrophy, thus causing a hypoxic environment. In turn, this form of cellular stress could increase the expression of the hypoxia-inducible transcription factor-1 (HIF-1) gene, which, through various signaling cascades, may result in an increase in the efficiency of the complex IV enzyme of the electron transport chain [61, 62]. Although an attractive hypothesis, it seems that studies that have investigated the effects of hypoxia on oxidative function with resistance training have not supported this model. One study investigated the mitochondrial response of eight weeks of resistance training in 16 male subjects who performed resistance training in either a normoxic environment or a hypoxic environment (14.4 % O_2) [63]. Research-

ers observed both training environments resulted in no change in PGC-1α mRNA and protein content, and a significant decrease in citrate synthase activity. Additionally, the authors did not observe an increase in HIF-1 mRNA content with the hypoxic exposure. Another study investigated the effects of a normoxic or hypoxic environment (13.5 % O_2) on endurance and resistance training adaptations for 10 weeks [64]. Investigators reported higher fatty acid oxidation capacity in both normoxic and hypoxic conditions with both training interventions. Furthermore, there was an increase in oxidative potential in both training environments. However, these researchers did not measure HIF-1 mRNA or protein levels, so it is possible the hypoxic-like environment did not stimulate a physiological hypoxic response. Another study has also reported four weeks of resistance training increased maximal power output regardless of normoxic or hypoxic exposure during exercise [65]. Additionally, the authors observed a significant increase in citrate synthase activity and state 3 respiration rates in normoxic resistance training environment, which again suggests that resistance training in lieu of hypoxia may not stimulate appreciable mitochondrial adaptations. Others have also investigated the effects of low-load resistance training (with or without blood flow restriction) to failure for six weeks in a within-subject design [66]. Both legs had similar muscle strength and size increases. However, mitochondrial respiratory capacity from vastus lateralis muscle biopsies increased only in the leg without blood flow restriction. These data further support the above statement that hypoxia, even transiently, does not facilitate mitochondrial changes with resistance training.

As with the few studies that have examined the effects of resistance training on mitochondrial function, there is also a paucity of data regarding alterations in mitochondrial dynamics with resistance training. A recent publication reported the response of mitochondrial dynamics markers with high-load, low-repetition training compared to low-load, high-repetition training and a work-matched intensity to the high-load, low-repetition training [67]. Researchers reported that the muscle protein content of the mitochondrial fusion marker OPA1 was significantly increased in the low-load, high-repetition individuals compared to pre-intervention and other groups. Additionally, the mitochondrial fission marker DRP1 was significantly higher post-intervention in the work-matched individuals. The low-load, high-repetition group had higher protein content of the mitochondrial fission marker DRP1 and FIS1 post-intervention. Furthermore, FIS1 was significantly higher compared to high-load, low-repetition training post-intervention. Lastly, researchers reported the MFN2/DRP1 ratio increased significantly in the high-load, low-repetition group post-intervention. These results suggest that regardless of the load, repetition to failure causes a positive response on mitochondrial dynamics to maintain mitochondrial structures. Animal studies have also observed an increase in OPA1 protein levels with chronic 4-week electrical stimulation; however these studies did not see a response to any mitochondrial fission proteins [68]. These animal studies also have observed an increase in protein expression of complex III that parallels the human response of an increase in protein content of COXIV with high-load and low-load resistance training [67].

Numerous reports suggest resistance training does not decrease and may even increase VO₂max [69–71]. Thus, it is unlikely that resistance training-induced mitochondrial dilution leads to functional deficits in aerobic capacity. One potential explanation as to how resistance training may increase VO₂max in lieu of citrate synthase activity deficits is that citrate synthase activity (or other enzyme activities) typically are assessed in crude muscle homogenates and the results are normalized to total protein content. For example, for a given pre- and post-resistance-training comparison, if contractile proteins (e. g., actin, myosin, etc.) increased due to hypertrophy and citrate synthase activity remained constant or even increased (albeit to a lesser extent than contractile proteins), then a mitochondrial dilution effect will be detected but respiration capacity (i. e., VO₂max) could still be equal/higher.

Collectively, much of the literature that has examined mitochondrial content via transmission electron microscopy or citrate synthase activity suggests resistance training decreases mitochondrial volume. However, certain studies also suggest resistance training enhances mitochondrial function, potentially though affecting complexes of the electron transport chain. It should also be noted that many of the studies above that have observed decreases in mitochondrial volume have examined young, healthy males. Therefore, it is possible that resistance training may elicit differential mitochondrial adaptations depending on age and health of the individual, and this is discussed in greater detail below. Furthermore, it is possible the discrepancy in results reported is due to different training paradigms. High-load, low-repetition training may elicit a different response to the mitochondria compared to low-load, high-repetition training; specifically, low-load, high-repetition training may stimulate more profound mitochondrial adaptations due to the higher volumes being "aerobic-like." This phenomenon is often observed in elderly individuals and will be discussed in greater detail below.

Mitochondrial adaptations to resistance training in older individuals

Sarcopenia is characterized by a loss of muscle mass and a decrease in strength that results in a poor ability to function [72–74]. Functional declines in aging might be caused by a decrease in aerobic capacity seen [75]. Decreases in muscle strength and aerobic capacity lead to a poorer quality of life, which contributes to an increase cardiovascular disease and frailty [72, 73, 76]. Previous reports have found that resistance training in older adults increases muscle mass and strength, thus combating sarcopenia [24, 25].

The mitochondrial theory of aging, also known as the free radical theory of aging, has also been of great interest in aging research. This theory suggests that as aging continues, an increase in reactive oxygen species production results in an accumulation of oxidative damage to lipids, proteins, and DNA [77–79]. Additionally, the model posits that mitochondrial dysfunction arises over the lifespan given that mitochondrial DNA is highly susceptible to oxidative damage. During aerobic respiration, reactive oxygen species are produced at eleven distinct sites, but complex I and III of the electron transport chain are commonly recognized as the major sites [80–82]. In general, superoxide is rapidly converted into hydrogen peroxide via superoxide dismutase 2 [80]. Hydrogen peroxide is capable of localizing to the cytosol to react with other cellular structures and organelles [80]. This oxidative damage is suggested to contribute to the aging process [77, 78].

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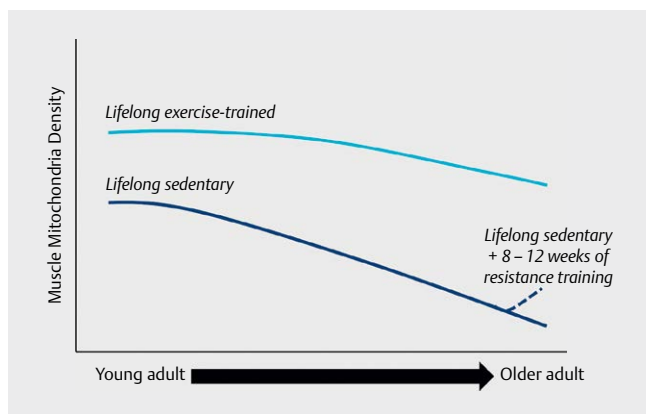
▶ Fig. 2 Simple illustration summarizing how exercise training can maintain (in lifelong exercise-trained individuals) or increase skeletal muscle mitochondria density (in lifelong sedentary individuals that participate in resistance training).

Although the evidence is limited, some studies have examined how resistance training affects markers of skeletal muscle oxidative stress as well as mitochondrial function in older individuals. Parise et al. [28] investigated the effects of whole-body resistance training for 14 weeks in elderly men and women on oxidative damage markers, antioxidant enzyme activity, and electron transport chain complex activity. The researchers observed a significant increase in complex IV activity and complex IV/complex I and complex III ratio, suggesting an increase in electron transport chain efficiency. Using the hydraulic theory as an analogue of the electron transport chain [83], the higher activity of complex IV drives the relationship of complex IV/complex I and complex III ratio as observed by Parise et al. [28]; this allows for a greater flux down the electron transport chain. This increase in oxygen utilization at complex IV allows for increased delivery of electrons at complex I and II due to the decrease in "electron backup" at complex IV. These events may result in a decrease in the electron leakage and, potentially, a reduction in oxidative stress. Parise et al. [28], also noted no change in the protein content of the antioxidants catalase and superoxide dismutase 1 and 2. In a follow-up study, Parise at al. [29] observed a significant increase in catalase and superoxide dismutase 1 enzyme activities. Collectively, both studies suggest that resistance training in older individuals results in: a) direct changes in electron transport chain complex activities, and b) an increase in catalase and superoxide dismutase 1 enzyme activities. These findings re-iterate that examining mitochondrial enzyme activities, rather than the protein content of these enzymes, may yield more insightful findings. More recently, Holloway et al. [84] determined how resistance training affects ADP sensitivity in elderly individuals. These researchers examined 10 healthy old males who partook in a 12-week resistance training program and compared the metabolic skeletal muscle profile of these individuals to 10 healthy younger males. Mitochondrial respiration was lower and hydrogen peroxide emission, an indirect measure of the generation of reactive oxygen species, was greater in older versus younger participants. Additionally, although resistance training caused an increase in ADP sensitivity, the oxidative state was not altered as determined

by the lack of change observed in reactive oxygen species production. The authors did observe a significant increase in maximal respiration (state 3) with resistance training, albeit there were no significant changes in the respiratory control ratio.

Further, a study conducted by Robinson et al. [85] determined the effects of twelve weeks of resistance training, high-intensity interval training, and combined training on exercise adaptations in younger and older participants. Whereas younger individuals in the high intensity interval training group experienced increases in VO_2max, this response was impaired (but still increased) in the older participants. Additionally, younger or older individuals in the resistance training group did not experience alterations in VO_2max or alterations in state 3 respiration for complexes I and II, and the mitochondrial DNA copy number decreased in both groups, which further supports mitochondrial dilution model. However, a significant increase in mitochondrial protein fractional synthesis rates and increases in various mitochondrial proteins (determined via proteomics) were observed following the resistance training intervention in older individuals. Not all studies agree that resistance training can cause a change to skeletal muscle oxidative capacity in older individuals. For instance, one study reported no change in skeletal muscle oxidative capacity in older males that resistance-trained for 12 weeks [86]. The authors also reported that training did not affect mRNA levels of PGC-1α, TFAM, or PPARδ, and citrate synthase activity remained unaltered. The authors did acknowledge the limitations of using a very healthy group of older individuals and individuals who were on statins, which may have affected their results. In this regard, statins have been reported to have deleterious effects on skeletal muscle mitochondria [87, 88], but it has also been reported that resistance training can help counter the increase in ROS observed in the skeletal muscle of individuals who have taken statins [89].

Collectively, the studies above largely indicate that resistance training facilitates positive redox and mitochondrial adaptations in older individuals. Although typically not reported, it is notable that pre-intervention activity levels may play an appreciable role in the mitochondrial adaptations to resistance training. Alternatively stated, resistance training may stimulate enough of an energy demand to facilitate appreciable mitochondrial adaptations in older individuals existing in a state of low habitual physical activity prior to training. **Figure 2** illustrates this concept, although more research is needed to validate this hypothesis.

Future research directions

Although decades of research have been devoted to the hypertrophic and strength adaptations that occur in response to resistance training [15, 18, 53, 90], much more research is needed to elucidate mitochondrial adaptations. One current limitation is that few studies have investigated the effects of resistance training on mitochondrial adaptations in females [91]. Although there may be no appreciable gender differences in response to resistance training, this remains to be determined. Additionally, although several studies cited herein suggest a dilution of mitochondria occurs with resistance training, there is equivocal evidence to support this notion [34, 53, 56]. We posit that it is currently unclear how resistance

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training affects mitochondrial biogenesis, and this is likely a result of different studies utilizing different training paradigms as well as methods to quantify mitochondria. It seems logical that high-volume resistance training likely has a greater impact in increasing mitochondrial biogenesis compared to high-load resistance training, given that the former style of training leads to greater metabolic perturbations (e. g., greater increases in blood lactate) [55, 92, 93]. Thus, continuing to examine how higher volume versus higher load resistance training affects markers of mitochondrial biogenesis is warranted. Although a plethora of evidence does suggest that mitochondrial dilution may occur with resistance training, more studies that include measurements of mitochondrial function via permeabilized fibers would provide a more comprehensive perspective regarding how training affects mitochondrial adaptations. Additionally, given that mitochondrial dynamics play a role in biogenesis and network expansion, future research is needed to determine how resistance training affects markers of mitochondrial fission and fusion as well as the mitochondrial reticulum [94–96]. Specifically, there have been differences in mitochondrial reticulum volume between mice and humans, suggesting that any changes that may have been observed in a mouse model may not translate to adaptations of the mitochondrial reticulum seen in humans [94]. The ability of the skeletal muscle mitochondria to possess proactive and reactive mechanisms for protection (i. e., mitochondrial dynamics, for more details please refer to [95]) suggests an intricate series of events in regard to electrical conductance and mitochondrial fission and fusion that need to be elucidated to be able to further understand how the stress of exercise affects the mitochondrial reticulum adaptations.

Conclusions

Overall, many of the investigations cited herein have contributed to our understanding of mitochondrial adaptations to resistance training. However, given that most of the resistance training research has focused on hypertrophic and strength adaptations, the examination of mitochondrial adaptations to resistance training is still in its infancy. Indeed, future research endeavors that continue to examine novel mitochondrial markers as well as mitochondrial function in permeabilized muscle fibers will continue to advance our current understanding of mitochondrial adaptations to resistance training.

Conflict of Interest

The authors declare that they have no conflict of interest.

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