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IMPACT OF PHYSICAL TRAINING ON MITOCHONDRIAL RESPIRATORY COMPLEX IN AGING SKELETAL MUSCLE

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ABSTRACT
There is an inverse relationship between age and muscle function, where both muscle strength and mass decline as an individual gets older. The gradual decline in both aspects can lead to mobility disabilities and premature mortality. The deterioration of skeletal muscle mitochondria is believed to be a major contributor to these events. Adopting an approach such as regular physical training could slow down this deterioration in mitochondrial function and alleviate age-related effects in humans. The present review focuses on articles published within the past ten years, specifically addressing physical training and the mitochondrial respiratory complex of skeletal muscle in older adults. A total of six studies were evaluated, comprising three cross-sectional studies, one follow-up study, one case-control study, and one interventional study. This review proposed that physical training can enhance the adaptability of skeletal muscle mitochondria in older individuals, indicating that the decline in aging muscle is not entirely due to the natural aging process. However, further research is required to explore whether different training protocols and durations yield similar improvements in mitochondrial function of skeletal muscle.

Keywords: physical training; exercise; mitochondrial respiratory complex; skeletal muscle; aging

INTRODUCTION

The global population of individuals aged 65 years and older is increasing expeditiously. It is projected that by 2050, this demographic will be twice as large as in 2021, growing from 761 million to 1.6 billion.[1] Starting in the fourth decennaries of life, muscle mass and strength gradually decline and accelerate with advancing age.[2] The gradual reduction of physical function and muscle mass is one of the distinct features associated with aging that can result in mobility disabilities and premature mortality.[3,4] Multiple biological mechanisms have been suggested to reveal the progression of this event. However, dysfunction of skeletal muscle mitochondria is hypothesized to pose a significant part in the decrease of muscle mass and function.[5,6]

Mitochondria are the primary organelles accountable for energy production within cells and play a crucial role in various biological activities related to growth, metabolism, and restoration of skeletal muscle. Mitochondrial dysfunction refers to a range of processes including changes in the structure and number of mitochondria, as well as changes in the function of the complexes involved in protein synthesis within mitochondria, the electron transport chain, and pathways of degradation.[7] The number and density of mitochondria, alongside their enzyme activities and respiration, decrease with age in skeletal muscle.[8]

Short-term physical training has been indicated to help sustain the function of mitochondria in the aging mouse muscle and the enzyme activity of the skeletal muscle in humans.[8] Furthermore, other studies have indicated that physical training can increase both the content and function of mitochondria in young and aged individuals.[5,9] In addition to boosting mitochondrial content and function, physical training also improves overall muscle mass, myofiber size, muscle quality, and helps attenuates age-related decline in muscle strength.[10]

This review has two objectives. The first is to outline the alterations that happened on skeletal muscle as a result of aging, while the second is to examine how physical training can mitigate mitochondrial dysfunction in older individuals.

METHODS

The sources of this literature review are research articles obtained from electronic journal databases such as Google Scholar, PubMed, and Scopus. The used keywords are "physical training", "exercise", "mitochondrial respiratory complex", "skeletal muscle", and "aging". The research articles focus on the relationship between physical training and mitochondrial respiratory complex of skeletal muscle in older adults, conducted in the last ten years (2013–2023). The selection criteria for the articles do not impose any language restrictions, allowing articles in various languages, including Indonesian, English, and other languages. A total of 17,599 articles were initially identified. Following the selection process, five studies were deemed eligible for inclusion in this review. The exclusion criteria encompassed studies conducted on animals and researches published prior to 2013.

RESULTS

Table 1 presents a summary of the results obtained from the inclusion of five eligible studies in this review.

Table 1. Effect of physical training on mitochondrial respiratory complex of skeletal muscle in older individuals

Reference	Study design	Subjects	Intervention	Mitochondrial respiratory complex
Ringholm S et al., 2023	Cross-sectional study	10 young males who engage in regular physical activity (20–32 years) 10 aged males (62–73 years) 6 moderately endurance exercised trained-aged males (62–73 years) 6 highly endurance exercised trained-aged males (62–73 years)	-	The vastus lateralis muscle of highly trained elderly males have been shown to contain a greater amount of complex I (subunit NDUFB8), complex II (subunit SDHB), complex III (subunit UQCRC2), complex IV (subunit MTCO1), and complex V (subunit ATP5A) compared to untrained young, untrained elderly, and trained elderly males.
Wyckelsma V et al., 2017	Follow up study	15 young adults 8 older adults (69.9 ± 3.8 years)	Cycling. 3 times a week for 12 weeks	High-intensity interval training (HIT) elevates complexes I, II, IV, and V of mitochondria, but did not result in an elevation in complex III.
Grevendonk L et al., 2021	Cross-sectional study	17 aged individuals with regular level of physical activity (71 years) 18 aged individuals with high level of physical activity (68 years) 6 aged individuals with diminished physical function, impairment, or low level of physical activity (71 years)	-	The protein expression levels of OXPHOS complex I and III were markedly raised in the highly active individuals compared to the normally active individuals. Additionally, the highly active individuals demonstrated higher protein expression levels of complex II and complex IV compared to both normally active and impaired individuals.
Joanisse S et al., 2020	Cross-sectional study	8 aged males (67 ± 2 years) 8 aged male cyclists (65 ± 5 years)	-	The protein content of complexes I, II, and IV revealed a 7.1-, 1.9-, and 1.3-fold increase, in the aged male

		9 young males (21 ± 3 years)		cyclists compared to the aged males, and a 5.6-, 2.1-, and 1.2-fold increase, compared to the young males. However, there were no notable differences in the protein content of complexes III and V among the groups.
Broskey N et al., 2014	Case-control study	14 older adults who engage in consistent endurance training (60–80 years) 14 sedentary older adults (60–80 years)	-	The subjects who participate in endurance training exhibited considerably increased levels of electron transport chain (ETC) complexes I, IV, and V, as well as in vivo oxidative phosphorylation capacity.
	Interventional study	6 sedentary older males (60–80 years) 4 sedentary older females (60–80 years)	Aerobic training. Minimum of 3 sessions a week for 16 weeks	Aerobic training promotes the levels of complexes III, IV, and V, accompanied by a pronounced inclination towards up-regulation of complex I.

DISCUSSION

a. Skeletal muscle mitochondria in aging

Skeletal muscle is known to perform a variety of functions such as maintaining body posture, aiding movement, producing heat, and regulating glucose levels in the body, which help in preventing mobility disabilities and early mortality.[4] Older individuals commonly exhibit changes in skeletal muscle metabolism due to a sedentary lifestyle.[13] The decrement in the skeletal muscle mass starts to develop in the third or fourth decennaries of life and roughly 10% of muscle mass is lost by the age of 50. By the seventh and eighth decennaries, there is an annual reduction of about 0.7%–0.8% of lower limb muscles in both men and women. In parallel with muscle mass, increasing age is also followed by a decline in muscle strength and regenerative capacity.[10]

While decreased skeletal muscle function has multiple causes, compelling experimental evidence indicates that the buildup of mitochondrial dysfunction is a substantial factor in the aging of muscle.[6,14] Skeletal muscle mitochondria are flexible structures, which can adapt and remodel their volume, structure, and function, as compensation for chronic training, inactivity, aging, and illness.[10,14–16] Constant remodeling of mitochondria involves several processes such as biogenesis, fusion, fission, and mitophagy. These processes are crucial for maintaining the functional integrity of mitochondria.[14] In aging muscle, morphological changes develop, which may result from imbalanced mitochondrial dynamics, where the rates of fusion and fission are not properly regulated.[17]

Furthermore, age-related oxidative stress induced by mitochondria is also thought to precipitate electron transport chain (ETC) dysfunction, reduced membrane potential, and activation of apoptotic pathways.[17] Although there is no consensus on whether aging affects the overall content of mitochondria, many studies have shown that as individuals age, mitochondrial dysfunction becomes more prominent. This can manifest in various age-related mitochondrial impairments, such as decreased respiration, protein synthesis, and maximal ATP production rates.[17–20]

b. Effect of physical training on skeletal muscle mitochondria in aging

The inner mitochondrial membrane contains five molecular complexes that play a crucial role in oxidative phosphorylation (OXPHOS), the mechanism by which mitochondria produce ATP, an essential source of cellular energy. These complexes are known as NADH ubiquinone oxidoreductase/NADH dehydrogenase (complex I), succinate ubiquinone oxidoreductase/succinate dehydrogenase (complex II), ubiquinol cytochrome c oxidoreductase/cytochrome bc_1 complex (complex III), cytochrome c oxidase (complex IV), and ATP synthase (complex V).[21] The work of Holloszy (1967) showed that physical training can enhance the function and number of mitochondria

in muscles to fulfill the rising energy requirements of active cells. Since then, there have been conclusive proof that endurance exercise enhances muscle fitness by promoting oxidative enzyme activities, oxidative phosphorylation, and mitochondrial content in both young and aged people.[11]

Previous studies have used biochemical measures as an alternative to quantify mitochondrial content in muscle. These measures have revealed that physical training can increase sensitivity to ADP, which indicates a higher number of mitochondria per gram of muscle. Several research groups have started using various mitochondrial markers to evaluate mitochondrial adaptations to long-term exercise, including citrate synthase, succinate dehydrogenase (complex II), cytochrome c oxidase (COX; complex IV), and cardiolipin content (inner mitochondrial phospholipid) to assess the changes in overall mitochondrial content.[16] Deciphering whether the deterioration of skeletal muscle function is due to aging itself or a result of lifestyle and disease poses a challenge in research.[10] Although not as extensively studied, resistance training (RT) is a widely recognized approach for increasing muscle mass and fitness at any age, while endurance training stimulates mitochondrial adaptations.[14,22]

In this review, two researchers analyzed the association between physical training and mitochondrial dysfunction in older individuals. A cross-sectional study investigated how habitual endurance exercise training affects mitochondrial function and network connectivity in the skeletal muscle of older humans. This study involved 10 physically active young males, 10 aged males, and 12 healthy endurance exercise trained-aged males. The latter group was then categorized into two subgroups, moderately endurance exercised-trained and highly endurance exercised-trained, based on their skeletal muscle citrate synthase activity and performance on an endurance exercise test. The study discovered that the vastus lateralis of highly trained older individuals had greater quantities of complex I (subunit NDUFB8), complex II (subunit SDHB), complex III (subunit UQCRC2), complex IV (subunit MTCO1), and complex V (subunit ATP5A) compared to untrained young individuals, untrained older individuals, and moderately trained older individuals.[8]

Research conducted by Wyckelsma et al., (2023) on 15 young adults and 8 elderly participants analyzed the association between high-intensity training (HIT) and maintenance of mitochondrial components of skeletal muscle in aged individuals. The elderly participants were engaged in twelve weeks of HIT exercise, using a mechanically braked cycle ergometer three times a week. However, younger participants were not included in the HIT training program. A biopsy of the vastus lateralis muscle was obtained from all participants using a biopsy needle. For older subjects, this was done before the training program began and again 24-48 hours after their last training session. Using BN-PAGE analysis, there were no significant changes found in the number of mitochondrial complexes I–IV in the muscle of young and elderly participants. However, after the HIT training program, the levels of complexes I, II, IV, and V demonstrated an elevation in elderly participants, even though complex III was unaffected.[5] The findings of this study are somewhat different from the previous study, which reported an increase in all mitochondrial complexes.

A cross-sectional study executed by Grevendonk L et al., (2021) examined the potential of routine physical training in aged individuals to preserve mitochondrial function. A total of forty-one aged individuals were enlisted for this study and subsequently classified into three groups: 17 aged individuals with normal level of physical activity, 18 aged individuals with high level of physical activity, and 6 aged individuals with impaired physical function. The protein expression of OXPHOS complex I and III was found to be elevated in greatly active individuals compared to normally active individuals. Additionally, the protein expression of complex II and complex IV was higher in greatly active individuals when compared to both normally active and physically impaired individuals.[3]

In the study conducted by Joanisse et al., (2020), a comparison was made between three groups comprised of 8 elderly males, 8 elderly male cyclists, and 9 young males, in terms of mitochondrial gene expression and protein content. Male participants were included in the study based on their capability to complete a 100 km cycling distance in less than 6.5 hours, and they were required to have accomplished this task on two occasions within the three weeks preceding the testing. Young and elderly males were recreationally active and performed daily activities but did not participate in a formal exercise training program or engage in more than two weekly exercise sessions. Protein content analysis of each complex within the electron transport chain was conducted using immunoblotting techniques. The protein complexes I, II, IV of mitochondria demonstrated 7.1-, 1.9-, and 1.3-fold higher levels in

the elderly male cyclists compared to the elderly males and 5.6-, 2.1-, and 1.2-fold higher levels compared to young males.[11]

Broskey et al., (2014) executed three distinct studies, one of which was case-control study employed to compare active older adults with sedentary older adults. The case-control study comprised a group of 14 older adults who consistently engaged in endurance training, alongside another group of 14 sedentary older adults. Subjects in both groups were selected to match in terms of age and gender. The subjects provided self-reported information regarding their levels of physical activity, which was then used to classify them as either physically active or sedentary. Participants in case-control and interventional study categorized as physically active engaged in at least three structured endurance exercise sessions per week for a duration of one year or more. In contrast, sedentary individuals were characterized as those who participated in a structured exercise session no more than once per week. The physically active volunteers exhibited higher levels of electron transport chain (ETC) complexes I, IV, and V, as well as greater in vivo oxidative phosphorylation capacity, compared to the sedentary volunteers.[12]

An interventional study conducted by Broskey et al., (2014) explored the ability of skeletal muscle in sedentary older adults to adapt in response to aerobic (endurance) training. A group of six sedentary older males and four sedentary older females were included as participants. The participants were enrolled in a 16-week supervised aerobic program with a moderate intensity level. Sedentary individuals were instructed to participate in at least three supervised gym sessions per week. The duration of each session gradually increased from 30 to 60 minutes. Moderate intensity was defined as maintaining a heart rate (HR) at 75% of the subjects' maximum HR. Participants were given the flexibility to choose activities such as biking, walking, running, or rowing, as long as they stayed within their target HR range. It was recommended that at least 80% of the training time be spent on walking or biking. A post-intervention assessment revealed notable increases in the levels of complexes III, IV, and V. Additionally, there was a significant inclination towards up-regulation observed in complex I.[12]

CONCLUSION

As individuals age, there is a decline in the amount and concentration of mitochondria in the skeletal muscle, as well as a decrease in their enzyme activities and respiration. Moreover, the capacity of mitochondria to adapt their size, structure, and function, which is critical in response to long-term exercise, aging, disease, and inactivity, is also compromised. The decrement of this capacity is recognized to be influenced by aging. Skeletal muscle mitochondria exhibit some degree of adaptability in response to training in older individuals, indicating that the decay of aged skeletal muscle is not ascribed solely to the aging course itself, but also to age-related lifestyle changes, especially physical inactivity. Exercise, especially high-intensity interval training (HIT) and aerobic (endurance) training, can avert the deterioration of muscle metabolism and function.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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