INVITED REVIEW / DAVETLİ DERLEME

DOI: 10.4274/atfm.galenos.2024.84755
Ankara Üniversitesi Tıp Fakültesi Mecmuası 2024;77(4):303-310

BASIC MEDICAL SCIENCES / TEMEL TIP BİLİMLERİ

Exercise and Mitochondrial Function in Neurodegenerative and Demyelinating Diseases

Nörodejeneratif ve Demyelinizan Hastalıklarda Egzersiz ve Mitokondriyal Fonksiyon

Gökhan Burçin Kubat[1,2], İbrahim Türkel[3], İlknur Melis Durası[4]

[1]*University of Health Sciences Türkiye, Gülhane Institute of Health Sciences, Department of Mitochondria and Cellular Research, Ankara, Türkiye*
[2]*University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Ankara, Türkiye*
[3]*Hacettepe University Faculty of Sport Sciences, Department of Exercise and Sport Sciences, Ankara, Türkiye*
[4]*Istanbul Health and Technology University, Department of Molecular Biology and Genetics, İstanbul, Türkiye*

Abstract

Neurodegenerative and demyelinating diseases have a major impact on patient longevity and quality of life, creating a serious risk to life, health, and well-being. These diseases have been associated with poor and malfunctioning mitochondria in the central nervous system. Mitochondria are vital for several biological processes, including the production of energy and reactive oxygen species, the regulation of calcium levels within cells, and the control of programmed cell death. Alterations in mitochondrial activity have a significant impact on the most prevalent neurodegenerative and demyelinating disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS). Exercise has been shown to improve muscle function and contribute to the muscle-brain interaction via various signaling pathways and molecular mechanisms (myokines, extracellular vesicles, and bioactive molecules etc.). The stimulation and subsequent training of skeletal muscle is a crucial aspect of exercise, with proven benefits for mitochondrial function. It is now known that exercise is a non-pharmacological method of preventing and reversing neurodegeneration and brain deterioration. Regular exercise enhances the survival and neuroplasticity of neurons and improves the body's reactions to stress in terms of mitochondria. This review presents an overview of current knowledge on the role of normal mitochondrial function, including mitochondrial biogenesis, dynamics, and mitophagy, as well as exercise and mitochondrial function, in neurodegenerative and demyelinating disorders. In the following sections, we also discuss how exercise affects mitochondrial processes in disorders such as AD, PD, MS, and ALS.

Keywords: Exercise, mitochondria, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis

Öz

Nörodejeneratif ve demyelinizan hastalıklar, hasta ömrü ve yaşam kalitesi üzerinde büyük bir etki yaratarak yaşam, sağlık ve refah için ciddi bir risk oluşturmaktadır. Bu hastalıkların, merkezi sinir sistemindeki hasarlı ve normal fonksiyonu bozulmuş mitokondrilerle çok yakından ilişkili olduğu gösterilmektedir. Mitokondri, enerji ve reaktif oksijen türlerinin üretimi, hücrelerdeki kalsiyum seviyelerinin düzenlenmesi ve programlanmış hücre ölümünün kontrolü gibi çeşitli biyolojik süreçler için hayati öneme sahiptir. Bununla birlikte, mitokondriyal aktivitedeki değişiklikler, Alzheimer hastalığı (AD), Parkinson hastalığı (PD), multipl skleroz (MS) ve amyotrofik lateral skleroz (ALS) gibi yaygın nörodejeneratif ve demyelinizan hastalıklar için kritiktir. Egzersizin kas fonksiyonunu iyileştirdiği, çeşitli sinyal yolakları ve moleküler mekanizmalar (miyokinler, hücre dışı veziküller ve biyoaktif moleküller vb.) yoluyla kas-beyin etkileşimine katkıda bulunduğu gösterilmiştir. İskelet kasının uyarılması ve antrene edilmesi, mitokondriyal fonksiyon için kanıtlanmış faydaları olan egzersizin çok önemli bir yönüdür. Egzersizin nörodejenerasyonu ve beyin hasarını önlemek için farmakolojik olmayan bir yöntem olduğu artık bilinmektedir. Düzenli egzersiz, nöronların hayatta kalmasını, nöroplastisitesini artırır ve vücudun mitokondri açısından strese verdiği tepkileri iyileştirir. Bu derleme, mitokondriyal biyogenez, dinamikler ve mitofaji dahil olmak üzere normal mitokondriyal fonksiyonun yanı sıra egzersiz ve mitokondriyal fonksiyonun nörodejeneratif ve demyelinizan bozukluklardaki rolü hakkındaki mevcut bilgilere genel bir bakış sunmaktadır. İlerleyen bölümlerde, egzersizin AD, PD, MS ve ALS gibi bozukluklarda mitokondriyal süreçleri nasıl etkilediği de tartışılmıştır.

Anahtar Kelimeler: Egzersiz, mitokondri, Alzheimer hastalığı, Parkinson hastalığı, multipl skleroz, amyotrofik lateral skleroz

Address for Correspondence/Yazışma Adresi: Gökhan Burçin Kubat
University of Health Sciences Türkiye, Gülhane Institute of Health Sciences; Gülhane Training and Research Hospital, Department of Mitochondria and Cellular Research, Ankara, Türkiye
E-mail: gokhanburcin.kubat@sbu.edu.tr **ORCID ID:** orcid.org/0000-0003-3220-465X
Received/Geliş Tarihi: 26.09.2024 **Accepted/Kabul Tarihi:** 27.11.2024

Introduction

The prevalence of neurodegenerative and demyelinating diseases is on the rise in parallel with the extension of human life expectancy. These conditions have significant implications for patient survival and quality of life, presenting a substantial hazard to life, health, and well-being (1). The functioning of the brain is dependent on adenosine triphosphate (ATP) levels, which is produced in large quantities by mitochondria through oxidative phosphorylation (OXPHOS). Neurons have a high metabolic demand and limited capacity for regeneration, making them particularly susceptible to the deleterious effects of mitochondrial dysfunction (2).

Mitochondria are indispensable for numerous biological functions, including energy and reactive oxygen species (ROS) production, calcium homeostasis, and cell death (3). Several vital biological processes, including the transportation of proteins, the formation of neuronal cell membrane potentials, and the transmission of signals, are unable to take place in the absence of energy provided by mitochondria (4).

Exercise has been postulated as a non-pharmacological intervention capable of modifying both brain structure and function (5). Regular exercise has significant beneficial effects on mitochondrial structure formation, with high-intensity exercise resulting in greater improvements in OXPHOS efficiency (6).

This review will center on elucidating the functions of mitochondria, as well as examining the impact of exercise-induced improvements in mitochondrial health on neurodegenerative and demyelinating diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).

Mitochondria and Normal Mitochondrial Function

Mitochondria, which developed through bacterial endosymbiosis, share striking similarities with archeabacterium (7). Although there are different views, an α-proteobacterium was engulfed by a predecessor of the current eukaryotic cell, resulting in the formation of mitochondria (8). Mitochondria are widely acknowledged as primary energy providers for cellular functions (9), with ATP production specifically tied to the efficiency of OXPHOS (10). Vital biological processes, such as protein transport, neuronal cell membrane potential generation, and signal transmission, rely on the energy supplied by mitochondria (4).

Mitochondrial Biogenesis

Healthy cells typically undergo mitochondrial biogenesis, a unique process for maintaining number, function, and energy production (11) (Figure 1). This process requires the synchronized transcription and translation of nuclear and mitochondrial genes located in both the nucleus and mitochondria since more than 90% of mitochondrial proteins are encoded by nuclear genes (12). The processes that comprise mitochondrial biogenesis include the replication of mitochondrial DNA (mtDNA), the synthesis of nuclear-encoded mitochondrial proteins, and the production of the inner and outer mitochondrial membranes (OMMs) and mitochondrial-encoded proteins (13).

Two main routes that control mitochondrial biogenesis are the sirtuin 1 (SIRT1)-peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and the adenosine monophosphate (AMP)-activated kinase (AMPK)-PGC-1α axis (14). Increased cellular energy demand activates the evolutionary cellular sensor known as AMPK, and mitochondrial bioenergetics and AMPK are closely related (15). PGC-1α can be immediately phosphorylated and activated by AMPK. The increase in PGC-1α expression and mitochondrial biogenesis may be due to AMPK activation (16). Additionally, PGC-1α is activated by SIRT1 (17). In an epilepsy model, SIRT1 activation improved hippocampal activity in rats by enhancing the PGC-1α/mitochondrial antioxidant signaling pathway (18).

Mitochondrial Dynamics

A mechanism known as mitochondrial dynamics regulates the size and structure of mitochondria through a repeated fusion and fission cycles (19) (Figure 1). The optic atrophy 1 protein, crucial for maintaining mitochondrial cristae structure, controls fusion on the inner mitochondrial membrane, while mitofusin-1 (MFN-1) and MFN-2 manage fusion on the OMM (20). The main mediator of mitochondrial fission is dynamin-related protein 1 (DRP1). Mitochondrial fission normally occurs in the cytoplasm. Under stress conditions, the four main adaptor proteins that attach cytosolic DRP1 monomers to the OMM are: Mitochondrial fission factor, mitochondrial fission 1 protein and mitochondrial dynamics proteins, which bind DRP1 to the OMM (21). To alleviate cellular dysfunction, prevent tissue deterioration and restore function, strategies aimed at balancing mitochondrial dynamics hold promise.

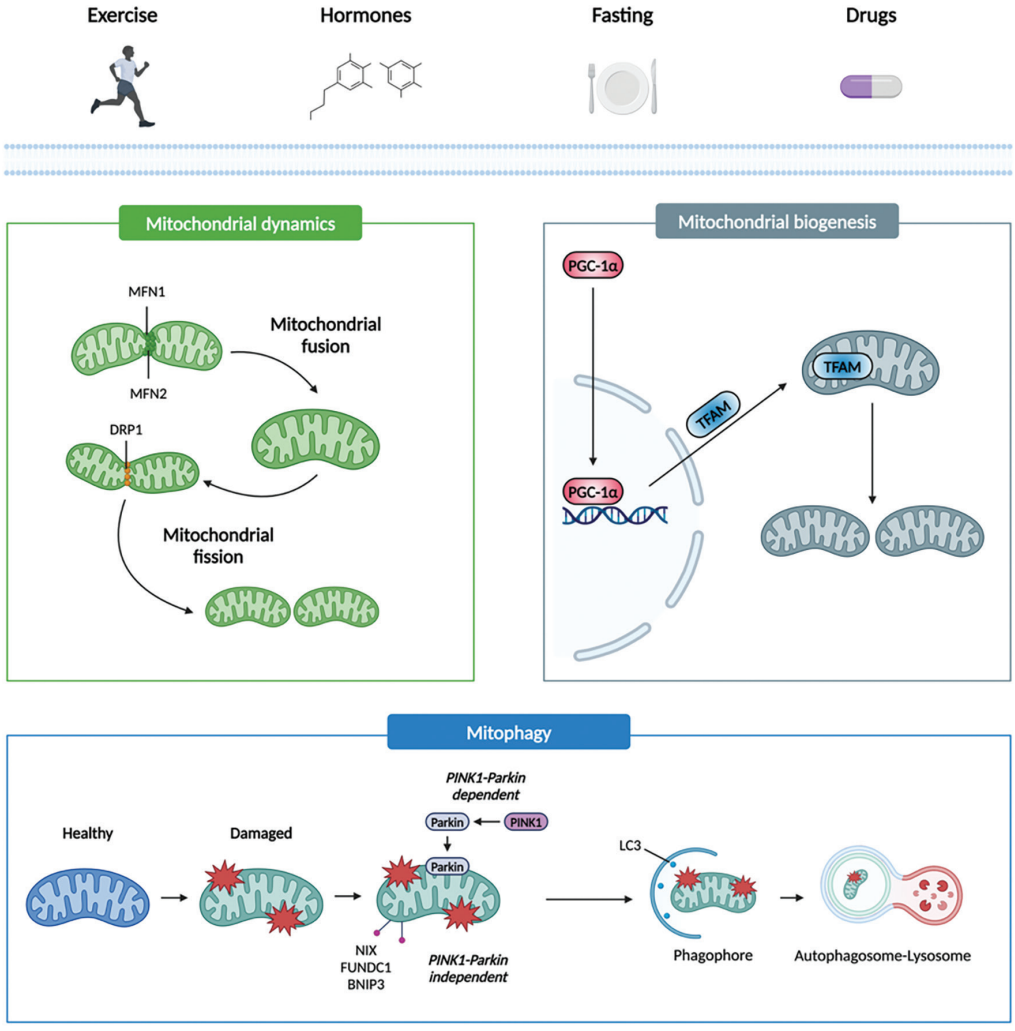

Figure 1: Components of mitochondrial adaptation to exercise, hormones, fasting, and drugs. Figure was created with BioRender.com

MFN1: Mitofusin-1, MFN2: Mitofusin-2, DRP1: Dynamin-related protein 1, PGC-1α: Proliferator-activated receptor gamma coactivator 1-alpha, TFAM: Transcription factor A, PINK1: Phosphatase and tensin homolog deleted on chromosome 10-induced putative protein kinase 1, NIX: NIP3-like protein X, FUNDC1: FUN14 domain containing 1, BNIP3: BCL2/adenovirus E1B 19 kDa protein-interacting protein 3, LC3: Microtubule-associated proteins 1A/1B light chain 3B

Mitophagy

The equilibrium between mitochondrial production and degradation determines mitochondrial mass, with mitochondrial biogenesis resulting in increased mitochondrial numbers, while a healthy mitochondrial population depends on the removal of defective mitochondria by mitophagy (22,23) (Figure 1). After the specific encapsulation of damaged mitochondria by the autophagosome, these mitochondria are transported to the lysosome where they fuse to form mature mitochondrial autolysosomes, which are then degraded by the lysosomes (24). Proteins located in the inner or outer membrane of mitochondria are known as mitophagy receptors, and contain microtubule-associated proteins 1A/1B light chain 3B (LC3)-interaction region (LIR) domain (25). Mitophagy receptor proteins selectively remove damaged mitochondria by interacting with the necessary autophagy protein LC3, mitophagy receptor proteins selectively destroy damaged mitochondria in response to various mitochondrial stresses, including reduction of mitochondrial membrane potential, oxidative stress, and other conditions, by interacting with the essential autophagy protein LC3 (26,27).

Damage or defect in the mitochondria results in the attachment of specific chemical markers, via the LC3 protein, to facilitate their identification and subsequent removal through a process known as mitophagy (28). Phosphatase and tensin homolog deleted on chromosome 10-induced kinase 1 (PINK1) accumulates on the OMM in the presence of cellular stress or mitochondrial depolarization, which attracts the E3 ubiquitin ligase Parkin (29). The OMM proteins mitofusins and other related proteins are ubiquitinated by the Parkin protein, which then forms polyubiquitin chains that serve as mitophagy signals (30).

The ubiquitin chains are bound by autophagy receptors such as optineurin and sequestosome-1, which interact with LC3 due to their LIR (31). This dual binding enables the mitochondria to be enclosed within an autophagosome for subsequent lysosomal destruction, thus maintaining cellular homeostasis. To fully realize the potential benefits of mitophagy without causing harm, there must be a balance in its activation.

The Effects of Exercise and Mitochondrial Dysfunction in Neurodegenerative and Demyelinating Diseases

The production of ATP and the quality control of mitochondria are of great importance in the context of neurodegenerative and demyelinating diseases, as these conditions are frequently characterized by mitochondrial dysfunction (32). Impaired OXPHOS results in a reduction of ATP levels, which in turn leads to energy deficits in neurons that are highly dependent on a steady energy supply (33). Concurrently, mitochondrial quality control mechanisms, including mitophagy, fission, and fusion, are disrupted, thereby exacerbating the accumulation of damaged mitochondria (34). For example, in PD, mutations in PINK1 and Parkin impair mitophagy, while in AD, altered mitochondrial dynamics contribute to the buildup of dysfunctional organelles (35,36). An understanding of these processes across various neurodegenerative and demyelinating diseases offers insight into common pathological mechanisms and potential therapeutic targets.

A growing body of research indicates that regular exercise can protect against chronic illnesses, delay the aging process, and improve overall health (37). Exercise induces perturbations in energy homeostasis in skeletal muscle, activating cellular signaling networks that facilitate the adaptation of skeletal muscle to the increased energy and oxygen demands associated with contraction-induced activity (38). High exercise capacity and mitochondrial function are clearly correlated, with mitochondria serving as the primary source of ATP and essential regulators of exercise capacity (39). Additionally, exercise enhances mitochondrial integrity and function by accelerating mitochondrial turnover, promoting efficient mechanisms for managing organelle turnover such as mitophagy and lysosome biogenesis (40). For example, exercise enhances mitochondrial functioning through its various physiological effects. Research indicates that exercise impacts hippocampal mitochondrial function, neuroplasticity, apoptosis, and increases levels of brain-derived neurotrophic factor (BDNF) (41).

Effects of Exercise and Mitochondrial Dysfunction in Parkinson's Disease

PD is defined by the gradual degradation of dopaminergic neurons, which finally results in a dopamine insufficient in the striatum (42). The pathophysiology of PD is closely linked to mitochondrial dysfunction and oxidative stress (43). A decrease in regulators of mitochondrial biogenesis has been demonstrated to result in a suppression of mitochondrial biogenesis in PD (44). Tissue samples from idiopathic PD patients who have post mortem have demonstrated higher mtDNA abnormalities, indicating mitochondrial malfunction in the disease (45). Several factors contribute to PD-associated mitochondrial dysfunction, including impaired mitochondrial biogenesis, elevated generation of ROS, impaired mitophagy, disrupted protein trafficking, and malfunctioning electron transport chain (ETC) (46).

After physical exercise, levels of BDNF, superoxide dismutase (SOD), and catalase increased in PD rats, while oxidative stress indicators for proteins and lipids decreased. These findings indicate that exercise improves oxidative stress markers and modulates the state of the neurochemicals (47) (Figure 2). Exercise training significantly reduced the loss of dopaminergic neurons in PD animals and improved neuronal and behavioral functions, accompanied by increased mitochondrial activity and neurotrophic factor levels in brain regions (37). In rats with PD, exercise training reduced oxidative stress, restore mitochondrial function, and enhanced dopaminergic neuron survival. This process may involve promoting mitochondrial turnover, including fission, fusion, and clearance, along with increasing mitochondria numbers (48). It has been demonstrated that treadmill exercise has shown promise in reducing α-synuclein accumulation in neurons and promoting the translation of biogenesis regulators and nuclear-encoded mitochondrial proteins. This may lead to an increase in mitochondrial biogenesis and the import of nuclear-encoded mitochondrial protein (49). Endurance exercise may be an effective method of enhancing cerebral mitochondrial biogenesis, thereby mitigating neural energy deficiencies in PD. In particular, treadmill training was observed to elevate or restore the levels of biogenesis regulators and import machinery (50).

Effects of Exercise and Mitochondrial Dysfunction in Alzheimer's Disease

AD is a neurodegenerative disease that affects millions of individuals worldwide and causes the brain to gradually and irreversibly deteriorate. ATP generation, the main energy source for cells, is impaired by mitochondrial dysfunction in AD. Amyloid beta-induced oxidative damage is connected to mitochondrial dysfunction in the early stages of AD (51). It is well established that amyloid beta can migrate to mitochondrial membranes, interfere with the ETC, produce more ROS, damage mitochondria, and impair normal neuron function (52). Increasing evidence suggests that defects in mitochondrial ETC

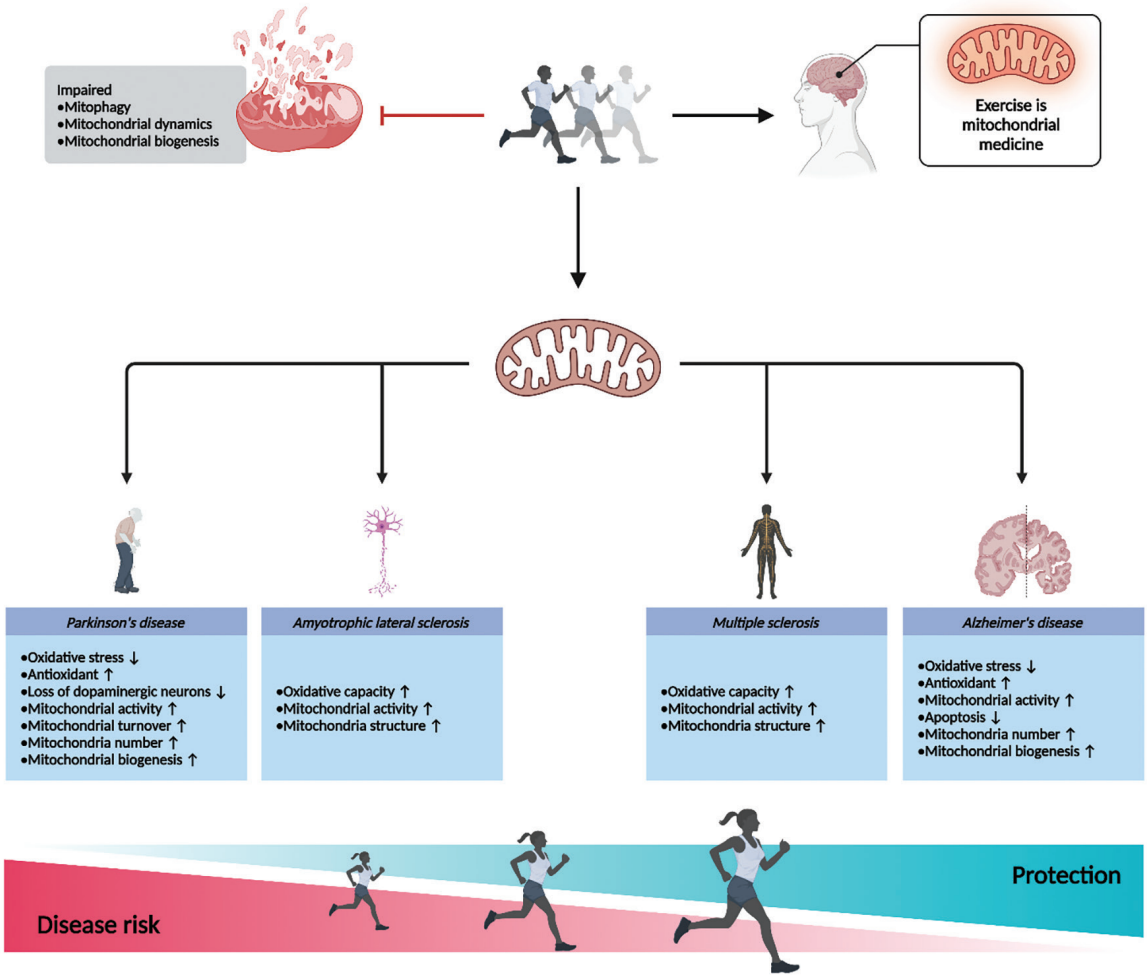

Figure 2: Relationship between exercise and mitochondrial dysfunction in neurodegenerative and demyelinating diseases. Figure was created with BioRender.com

enzymes and reduced efficiency of complex I and complex IV are associated with AD (53).

Exercise has been demonstrated to benefit several prominent symptoms of AD by regulating brain pathways associated with oxidative stress (54) (Figure 2). In addition, it has been shown that regular exercise significantly increases the metabolic rate and thus reduces the ROS level (55). While acute exercise may not have a significant effect on brain mitochondria, sustained exercise may decrease oxidative DNA damage and lipid peroxidation (56). Additionally, there has been evidence of elevation of mitochondrial antioxidant (SOD and catalase) activity in AD animal models treated to prolonged exercise (57). Six-day-a-week swimming exercise preserved the margins and cristae of the mitochondria, increased brain ATP generation, and enhanced synaptic density (58). The evidence suggests that exercise can serve as a therapeutic strategy to alleviate the deleterious effects of AD. These benefits are attributed to exercise's interactions with mitochondrial functions, including redox balance, enhancement of bioenergetics, apoptosis blocking, and inducement of mitochondrial biogenesis in AD.

Effects of Exercise and Mitochondrial Dysfunction in Multiple Sclerosis

MS is a long-term autoimmune disorder highlighted by demyelination, inflammation, neuronal death, and scarring (59). Mitochondrial dysfunction is increasingly recognized as a significant component of MS pathology, impacting the clinical course of the disease. Damage to mitochondria results in energy deprivation, leading to dysfunction in neuronal signal transmission (60). Oxidative damage, marked by the formation of oxidized lipids, proteins, and DNA, is observed in the process of cellular degeneration within the dynamic and progressively increasing lesions typical of MS (61). Inflammation in MS contributes to energy depletion and mitochondrial dysfunction, further exacerbating neuronal deterioration (62). MS also affects mitochondrial dynamics in neurons, including fission

and fusion processes. Defects in mitochondria and subsequent energy failure can disrupt other cellular processes, contributing to increased demyelination and inflammation in affected neurons and tissues (63).

It is well documented that people with MS benefit from regular exercise, which improves motor function, reduces fatigue, and enhances cardiorespiratory fitness (64) (Figure 2). Mitochondrial enzymes in individuals with MS have shown reduced succinate dehydrogenase activity across all types of muscle fibers, suggesting a greater reliance on anaerobic rather than aerobic oxidative ATP production compared to healthy individuals (65). Changes in muscle fiber dimensions and composition associated with MS are accompanied by alterations in muscle mitochondrial content (66). A cross-sectional study found a positive correlation between walking performance and physical activity levels in people with MS. The study results indicated that walking performance correlates positively with brain volume, fatigue levels, cognitive processing speed, and tract integrity (67).

Effects of Exercise and Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis

ALS, characterized by motor neuron atrophy in the nervous system, is the most common form of motor neuronopathy in adults (68). Substantial evidence links ALS pathology to progressive changes in mitochondrial structure, bioenergetics, and calcium homeostasis (69). Motor neurons derived from ALS patients exhibit altered structural features and mitochondrial clustering, characterized by enlarged and vacuolated organelles (70). ALS patients also demonstrate reduced activity in all complexes of the ETC, including complexes I, II, III, and IV (71). Excessive production of ROS in ALS contributes to oxidative damage across cellular components, particularly affecting mitochondria, which are highly susceptible to such damage (72). Furthermore, increased ROS generation promotes muscle atrophy in ALS (73).

It has been demonstrated that regular exercise can have beneficial effects on muscular strength and oxidative capacity in healthy individuals. Therefore, exercise can be regarded as a potentially viable therapeutic option for patients suffering from ALS (74) (Figure 2). Clinical trials suggest that exercise can enhance lung function and functional capacity in ALS patients, primarily demonstrated over the long term, with limited benefits observed in the short or medium term (75). It has previously been debatable whether exercise increases the risk of ALS (76). In ALS, it is the type IIB muscle fibers that are most vulnerable to the disease's progression. These fibers are responsible for anaerobic activity, and there is evidence that ALS is particularly associated with strenuous exercise (76-78). It has been demonstrated that swimming exercise results in modifications to the structure and function of mitochondria, which can be attributed to alterations in the concentration of mitochondrial cholesterol (79). Furthermore, numerous studies have indicated that individuals with ALS exhibit abnormal physiological responses to exercise (80). Prolonged periods of high-intensity exercise have been shown to exacerbate several adverse effects on the body, including motor neuron denervation, irreversible strength loss, and muscle degeneration (81). It has been suggested that moderate exercise programs may be beneficial for people with ALS, potentially impacting free radical balance and muscle fiber oxidation (82,83).

It is possible that excessive exercise may overload the antioxidant systems of ALS patients, which are already compromised, and increase the generation of ROS (84). This could result in further harm to nearby tissues and neurons. Moreover, the capacity to recuperate muscles following strenuous exercise is compromised by the progressive loss of motor neurons and ensuing muscular atrophy associated with ALS (85). The progression of the disease may be accelerated by overexertion, which can lead to increased fatigue and accelerate the degeneration of motor neurons (85). The findings of research conducted on animals and observations made by patients indicate that moderate, tailored exercise may improve quality of life and potentially slow the progression of symptoms (83). However, excessive or uncontrolled exercise has been shown to have adverse effects (81). It is therefore imperative that exercise regimens are tailored to the individual and designed to avoid overexertion to effectively manage ALS.

Conclusion

Exercise has been recognized as a non-pharmacological intervention with neuroprotective effects in neurodegenerative and demyelinating disorders. Its mechanism involves modulating multiple brain pathways, with mitochondria being a significant target organelle affected by physical activity. Exercise plays a crucial role in preventing and treating neurodegenerative and demyelinating diseases by interacting with mitochondrial mechanisms, including redox control, bioenergetics, reduced apoptosis, stimulation of mitochondrial biogenesis, and modulation of mitochondrial dynamics and mitophagy.

It is of the utmost importance that future studies concentrate on elucidating the complex relationships between human activity and mitochondrial function, particularly in the context of neurodegenerative and demyelinating disorders. An investigation into the influence of exercise on mitochondrial biogenesis, dynamics and quality control may facilitate the development of targeted treatment approaches. One promising avenue of research is the utilization of wearable technology, such as sensors, to monitor mitochondrial biomarkers and physiological responses in real-time. These techniques may enable the precise measurement of mitochondrial responses to

various exercise regimens, aiding in the optimization of duration and intensity for maximal benefit. These advancements may pave the way for the development of personalized therapies that enhance outcomes while reducing risks for susceptible groups.

Footnotes

Authorship Contributions

Concept: G.B.K., İ.T., İ.M.D., Design: G.B.K., İ.T., İ.M.D., Literature Search: G.B.K., İ.T., İ.M.D., Writing: G.B.K., İ.T., İ.M.D.

Conflict of Interest: There is no potential conflict of interest to declare.

Financial Disclosure: This study received no financial support.

References

1. López-Cuenca I, De Hoz R. Special issue: "Neurodegenerative diseases: recent advances and future perspectives". Biomedicines. 2024;12:1080.
2. Wu Y, Chen M, Jiang J, et al. Mitochondrial dysfunction in neurodegenerative diseases and drug targets via apoptotic signaling. Mitochondrion. 2019;49:35-45.
3. Rey F, Ottolenghi S, Zuccotti GV, et al. Mitochondrial dysfunctions in neurodegenerative diseases: role in disease pathogenesis, strategies for analysis and therapeutic prospects. Neural Regen Res. 2022;17:754-758.
4. Jordan J, de Groot PW, Galindo MF. Mitochondria: the headquarters in ischemia-induced neuronal death. Cent Nerv Syst Agents Med Chem. 2011;11:98-106.
5. Marques-Aleixo I, Beleza J, Sampaio A, et al. Preventive and therapeutic potential of physical exercise in neurodegenerative diseases. Antioxid Redox Signal. 2021;34:674-693.
6. Burtscher J, Romani M, Bernardo G, et al. Boosting mitochondrial health to counteract neurodegeneration. Prog Neurobiol. 2022;215:102289.
7. Javadov S, Kozlov AV, Camara AKS. Mitochondria in Health and Diseases. Cells. 2020;9:1177.
8. Lane N, Martin W. The energetics of genome complexity. Nature. 2010;467:929-934.
9. Harris DA, Das AM. Control of mitochondrial ATP synthesis in the heart. Biochem J. 1991;280:561-573.
10. Hroudová J, Fišar Z. Control mechanisms in mitochondrial oxidative phosphorylation. Neural Regen Res. 2013;8:363-375.
11. Popov LD. Mitochondrial biogenesis: An update. J Cell Mol Med. 2020;24:4892-4899.
12. Ploumi C, Daskalaki I, Tavernarakis N. Mitochondrial biogenesis and clearance: a balancing act. FEBS J. 2017;284:183-195.
13. Li PA, Hou X, Hao S. Mitochondrial biogenesis in neurodegeneration. J Neurosci Res. 2017;95:2025-2029.
14. Cantó C, Auwerx J. PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Curr Opin Lipidol. 2009;20:98-105.
15. Hardie DG. AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. Nat Rev Mol Cell Biol. 2007;8:774-785.
16. Birkenfeld AL, Lee HY, Guebre-Egziabher F, et al. Deletion of the mammalian INDY homolog mimics aspects of dietary restriction and protects against adiposity and insulin resistance in mice. Cell Metab. 2011;14:184-195.
17. Zhou Y, Wang S, Li Y, et al. SIRT1/PGC-1α signaling promotes mitochondrial functional recovery and reduces apoptosis after intracerebral hemorrhage in rats. Front Mol Neurosci. 2018;10:443.
18. Wang SJ, Zhao XH, Chen W, et al. Sirtuin 1 activation enhances the PGC-1α/mitochondrial antioxidant system pathway in status epilepticus. Mol Med Rep. 2015;11:521-526.
19. Kondadi AK, Reichert AS. Mitochondrial dynamics at different levels: from cristae dynamics to interorganellar cross talk. Annu Rev Biophys. 2024;53:147-168.
20. García-Peña LM, Abel ED, Pereira RO. Mitochondrial dynamics, diabetes, and cardiovascular disease. Diabetes. 2024;73:151-161.
21. Wang Y, Dai X, Li H, et al. The role of mitochondrial dynamics in disease. MedComm. 2023;4:462.
22. Dominy JE, Puigserver P. Mitochondrial biogenesis through activation of nuclear signaling proteins. Cold Spring Harb Perspect Biol. 2013;5:015008.
23. D'arcy MS. Mitophagy in health and disease. Molecular mechanisms, regulatory pathways, and therapeutic implications. Apoptosis. 2024;29:1415-1428.
24. Tang S, Geng Y, Lin Q. The role of mitophagy in metabolic diseases and its exercise intervention. Front Physiol. 2024;15:1339128.
25. Li S, Zhang J, Liu C, et al. The role of mitophagy in regulating cell death. Oxid Med Cell Longev. 2021;2021:6617256.
26. Onishi M, Okamoto K. Mitochondrial clearance: mechanisms and roles in cellular fitness. FEBS Lett. 2021;595:1239-1263.
27. Liu L, Li Y, Chen G, et al. Crosstalk between mitochondrial biogenesis and mitophagy to maintain mitochondrial homeostasis. J Biomed Sci. 2023;30:86.
28. Hamacher-Brady A, Brady NR. Mitophagy programs: mechanisms and physiological implications of mitochondrial targeting by autophagy. Cell Mol Life Sci. 2016;73:775-795.
29. Wang S, Long H, Hou L, et al. The mitophagy pathway and its implications in human diseases. Signal Transduction Target Ther. 2023;8:304.
30. Uoselis L, Nguyen TN, Lazarou M, et al. Mitochondrial degradation: mitophagy and beyond. Mol Cell. 2023;83:3404-3420.
31. Rogov V, Dötsch V, Johansen T, et al. Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy. Mol Cell. 2014;53:167-178.
32. Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther. 2012;342:619-630.
33. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, et al. Mitochondria and brain disease: a comprehensive review of pathological mechanisms and therapeutic opportunities. Biomedicines. 2023;77:2488.
34. Liu BH, Xu CZ, Liu Y, et al. Mitochondrial quality control in human health and disease. Mil Med Res. 2024;11:32.
35. Deas E, Wood NW, Plun-Favreau H. Mitophagy and Parkinson's disease: the PINK1-parkin link. Biochim Biophys Acta. 2011;1813:623-633.
36. Wang W, Zhao F, Ma X, et al. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener. 2020;15:30.
37. Lau YS, Patki G, Das-Panja K, et al. Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. Eur J Neurosci. 2011;33:1264-1274.
38. Reisman EG, Hawley JA, Hoffman NJ. Exercise-regulated mitochondrial and nuclear signalling networks in skeletal muscle. Sports Med. 2024;54:1097-1119.
39. Huertas JR, Casuso RA, Agustín PH, et al. Stay fit, stay young: mitochondria in movement: the role of exercise in the new mitochondrial paradigm. Oxid Med Cell Longev. 2019;7058350.
40. Joseph AM, Adhihetty PJ, Leeuwenburgh C, et al. Beneficial effects of exercise on age-related mitochondrial dysfunction and oxidative stress in skeletal muscle. J Physiol. 2016;594:5105-5123.
41. Seo JH, Park HS, Park SS, et al. Physical exercise ameliorates psychiatric disorders and cognitive dysfunctions by hippocampal mitochondrial function and neuroplasticity in post-traumatic stress disorder. Exp Neurol. 2019;322:113043.
42. Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, et al. The epidemiology of Parkinson's disease. Lancet. 2024;403:283-292.

43. Magaña JC, Deus CM, Giné-Garriga M, et al. Exercise-boosted mitochondrial remodeling in Parkinson's disease. Biomedicines. 2022;10:3228.
44. Perier C, Vila M. Mitochondrial biology and Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2:009332.
45. Henrich MT, Oertel WH, Surmeier DJ, et al. Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential. Mol Neurodegener. 2023;18:83.
46. Prasuhn J, Davis RL, Kumar KR. Targeting mitochondrial impairment in Parkinson's disease: Challenges and Opportunities. Front Cell Dev Biol. 2021;8:615461.
47. Tuon T, Valvassori SS, Lopes-Borges J, et al. Physical training exerts neuroprotective effects in the regulation of neurochemical factors in an animal model of Parkinson's disease. Neuroscience. 2012;227:305-312.
48. Chuang CS, Chang JC, Cheng FC, et al. Modulation of mitochondrial dynamics by treadmill training to improve gait and mitochondrial deficiency in a rat model of Parkinson's disease. Life Sci. 2017;191:236-244.
49. Koo JH, Cho JY. Treadmill exercise attenuates α-synuclein levels by promoting mitochondrial function and autophagy possibly via SIRT1 in the chronic MPTP/P-induced mouse model of Parkinson's disease. Neurotox Res. 2017;32:473-486.
50. Nhu NT, Cheng YJ, Lee SD. Effects of treadmill exercise on neural mitochondrial functions in Parkinson's disease: a systematic review of animal studies. Biomedicines. 2021;9:1011.
51. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med. 2008;14:45-53.
52. Aran KR, Singh S. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease–A step towards mitochondria based therapeutic strategies. Aging and Health Research. 2023;3:100169.
53. Manczak M, Park BS, Jung Y, et al. Differential expression of oxidative phosphorylation genes in patients with Alzheimer's disease: implications for early mitochondrial dysfunction and oxidative damage. Neuromolecular Med. 2004;5:147-162.
54. Radak Z, Marton O, Nagy E, et al. The complex role of physical exercise and reactive oxygen species on brain. Journal of Sport and Health Science. 2013;2:87-93.
55. Meng Q, Su C-H. The impact of physical exercise on oxidative and nitrosative stress: balancing the benefits and risks. Antioxidants. 2024;13:573.
56. Liu J, et al. Chronically and acutely exercised rats: biomarkers of oxidative stress and endogenous antioxidants. J Appl Physiol (1985). 2000;89:21-28.
57. Bernardo TC, Marques-Aleixo I, Beleza J, et al. Physical exercise and brain mitochondrial fitness: the possible role against Alzheimer's disease. Brain Pathol. 2016;26:648-663.
58. Pang R, Wang X, Pei F, et al. Regular exercise enhances cognitive function and intracephalic GLUT expression in Alzheimer's disease Model Mice. J Alzheimers Dis. 2019;72:83-96.
59. Haki M, Al-Biati HA, Al-Tameemi ZS, et al. Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. Medicine (Baltimore). 2024;103:37297.
60. Stys PK. General mechanisms of axonal damage and its prevention. J Neurol Sci. 2005;233:3-13.
61. Lassmann H, Van Horssen J. Oxidative stress and its impact on neurons and glia in multiple sclerosis lesions. Biochim Biophys Acta. 2016;1862:506-510.
62. Su K, Bourdette D, Forte M. Mitochondrial dysfunction and neurodegeneration in multiple sclerosis. Front Physiol. 2013;4:169.
63. Mao P, Reddy PH. Is multiple sclerosis a mitochondrial disease? Biochim Biophys Acta. 2010;1802:66-79.
64. Motl RW, Sandroff BM, Kwakkel G, et al. Exercise in patients with multiple sclerosis. Lancet Neurol. 2017;16:848-856.
65. Kent-Braun JA, Ng AV, Castro M, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. J Appl Physiol (1985). 1997;83:1998-2004.
66. Wens I, Dalgas U, Vandenabeele F, et al. Multiple sclerosis affects skeletal muscle characteristics. 2014;9:108158.
67. Orban A, Garg B, Sammi MK, et al. Effect of high-intensity exercise on multiple sclerosis function and phosphorous magnetic resonance spectroscopy outcomes. Med Sci Sports Exerc. 2019;51:1380-1386.
68. Kubat GB, Picone P. Skeletal muscle dysfunction in amyotrophic lateral sclerosis: a mitochondrial perspective and therapeutic approaches. Neurol Sci. 2024;45:4121-4131.
69. Muyderman H, Chen T. Mitochondrial dysfunction in amyotrophic lateral sclerosis - a valid pharmacological target? Br J Pharmacol. 2014;171:2191-2205.
70. Sasaki S, Iwata M. Mitochondrial alterations in the spinal cord of patients with sporadic amyotrophic lateral sclerosis. J Neuropathol Exp Neurol. 2007;66:10-6.
71. Wiedemann FR, Manfredi G, Mawrin C, et al. Mitochondrial DNA and respiratory chain function in spinal cords of ALS patients. J Neurochem. 2002;80:616-625.
72. Rego AC, Oliveira CR. Mitochondrial dysfunction and reactive oxygen species in excitotoxicity and apoptosis: implications for the pathogenesis of neurodegenerative diseases. Neurochem Res. 2003;28:1563-1574.
73. Zhou J, Li A, Li X, et al. Dysregulated mitochondrial Ca(2+) and ROS signaling in skeletal muscle of ALS mouse model. Arch Biochem Biophys. 2019;663:249-258.
74. Ferri A, Lanfranconi F, Corna G, et al. Tailored exercise training counteracts muscle disuse and attenuates reductions in physical function in individuals with amyotrophic lateral sclerosis. Front Physiol. 2019;10:1537.
75. Meng L, Li X, Li C, et al. Effects of exercise in patients with amyotrophic lateral sclerosis: a systematic review and meta-analysis. Am J Phys Med Rehabil. 2020;99:801-810.
76. Julian TH, Glascow N, Barry ADF, et al. Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. EBioMedicine. 2021;68:103397.
77. Ragagnin AMG, Shadfar S, Vidal M, et al. Motor neuron susceptibility in ALS/FTD. Front Neurosci. 2019;13:532.
78. Huisman MH, Seelen M, de Jong SW, et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2013;84:976-981.
79. Flis DJ, Dzik K, Kaczor JJ, et al. Swim training modulates skeletal muscle energy metabolism, oxidative stress, and mitochondrial cholesterol content in amyotrophic lateral sclerosis mice. Oxid Med Cell Longev. 2018;2018:5940748.
80. Siciliano G, Pastorini E, Pasquali L, et al. Impaired oxidative metabolism in exercising muscle from ALS patients. J Neurol Sci. 2001;191:61-65.
81. Lui AJ, Byl NN. A systematic review of the effect of moderate intensity exercise on function and disease progression in amyotrophic lateral sclerosis. J Neurol Phys Ther. 2009;33:68-87.
82. Kilmer DD. Response to aerobic exercise training in humans with neuromuscular disease. Am J Phys Med Rehabil. 2002;81(11 Suppl):148-150.
83. Fowler WM Jr. Role of physical activity and exercise training in neuromuscular diseases. Am J Phys Med Rehabil. 2002:81(11 Suppl):187-195.
84. Siciliano G, Chico L, Lo Gerfo A, et al. Exercise-related oxidative stress as mechanism to fight physical dysfunction in neuromuscular disorders. Front Physiol. 2020;11:451.
85. Scaricamazza S, Salvatori I, Ferri A, et al. Skeletal muscle in ALS: an unappreciated therapeutic opportunity? Cells. 2021;10:525.