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EXERCISE- INDUCED MITOCHONDRIAL ADAPTATIONS AND THEIR ROLE IN PREVENTIVE MEDICINE

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ABSTRACT

Background. Mitochondrial dysfunction is a key mechanism underlying chronic diseases such as type 2 diabetes, cardiovascular disease, neurodegenerative disorders, and age-related conditions. In contrast, exercise training promotes mitochondrial adaptations that improve metabolic health and physical performance, making mitochondrial health an important therapeutic target.
Aim. The aim of this review was to evaluate the current evidence on exercise-induced mitochondrial adaptations and their role in disease prevention, focusing on molecular mechanisms linking sports science with preventive medicine.
Materials and Methods. A literature review was conducted using PubMed, Web of Science, and SPORTDiscus databases. Studies published between 2019 and 2026 were selected according to predefined inclusion and exclusion criteria and analyzed qualitatively.
Results. Evidence shows that exercise training increases skeletal muscle mitochondrial content and activates pathways regulating biogenesis, dynamics, and quality control. These adaptations also occur in vascular, cardiac, and neural tissues, enhancing oxidative capacity, metabolic flexibility, and antioxidant defense, particularly in type 2 diabetes prevention. However, differences in exercise protocols and outcome measures limit conclusions regarding optimal training prescriptions.
Conclusions. Mitochondrial adaptations are a major mechanism linking exercise to disease prevention. Different exercise modalities induce distinct mitochondrial responses, supporting precision exercise prescription in athletic and clinical populations.

KEYWORDS
Mitochondrial Biogenesis, Exercise Training, Mitochondrial Dynamics, Cardiovascular Disease, Metabolic Health, Preventive Medicine

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1. Introduction

1.1 The Mitochondrial Paradigm in Health and Disease

Mitochondria serve as cellular powerhouses responsible for ATP production through oxidative phosphorylation, but their functions extend far beyond energy metabolism. These dynamic organelles regulate calcium homeostasis, redox signaling, apoptosis, metabolic substrate utilization, and inter-organellar communication.[3][10] The heart, skeletal muscle, brain, and kidneys, organs with the highest metabolic demands, rely most heavily on mitochondrial function, making them particularly vulnerable to mitochondrial dysfunction.[9][11] Mitochondrial dysfunction has emerged as a common pathophysiological feature underlying numerous chronic diseases, representing a potential "common root of noncommunicable chronic diseases." In metabolic syndrome and type 2 diabetes mellitus (T2DM), reduced mitochondrial oxidative capacity, decreased mitochondrial content, and impaired mitochondrial dynamics contribute to ectopic lipid accumulation and insulin resistance.[11][6][12][13] Skeletal muscle mitochondrial dysfunction is a key driver of insulin resistance and T2DM progression, with the relationship appearing bidirectional , as reduced mitochondrial function predisposes to insulin resistance, while insulin resistance further impairs mitochondrial biogenesis.[6][12] In cardiovascular disease, mitochondrial dysfunction contributes to endothelial dysfunction, cardiomyocyte death, and heart failure progression through excessive reactive oxygen species (ROS) production, impaired calcium handling, and defective mitochondrial quality control.[8][14][15] Vascular mitochondria constantly integrate environmental signals and respond accordingly to match vascular function to metabolic requirements, while mitochondrial dysfunction contributes to vascular aging and pathologies including atherosclerosis, stenosis, and hypertension.[8] Mitochondria serve as the central hub linking exercise to enhanced cardiac function, governing cellular survival and death through regulation of respiration, dynamics,

calcium homeostasis, inflammatory signaling, and oxidative stress.[16] In neurodegenerative diseases, particularly Alzheimer's disease (AD), mitochondrial dysfunction plays a central role in disease development.[9][17] Neurons, as highly specialized post-mitotic cells with higher bioenergetic demands, are inherently dependent on mitochondria. The accumulation of dysfunctional mitochondria has been reported as an early stage that significantly facilitates AD progression, causing bioenergetic deficiency, intracellular calcium imbalance, and oxidative stress, thereby aggravating β-amyloid accumulation and Tau hyperphosphorylation.[9][17] Impaired mitophagy has been identified in the hippocampus of AD patients, in induced pluripotent stem cell-derived human AD neurons, and in animal AD models, with mitophagy stimulation reversing memory impairment through PINK1-, Parkin-, or DCT-1-dependent pathways.[18] During aging, mitochondrial dysfunction is characterized by reduced mitochondrial content, impaired respiratory function, increased ROS production, and accumulation of mtDNA mutations, contributing to sarcopenia, frailty, and age-related metabolic decline.[7][19] Aging is intimately associated with progressive dysregulation of the mitochondrial quality control (MQC) network, encompassing mitochondrial biogenesis, dynamic remodeling, selective autophagy, proteostasis maintenance, and coordinated mitochondrial-organelle communication.[5] Physical inactivity represents a major risk factor for global mortality and is linked to chronic disorders whose treatment absorbs substantial healthcare costs in developed countries.[20] Conversely, exercise training represents the most potent non-pharmacological intervention for improving mitochondrial health across multiple tissues.[3][5][7]

1.2 Exercise as a Mitochondrial Stimulus

Exercise induces transient metabolic perturbations that serve as signals for mitochondrial adaptation. During contractile activity, skeletal muscle experiences energetic stress (increased AMP:ATP ratio), nutrient stress (glycogen depletion), oxidative stress (ROS production), and calcium flux, all of which activate signaling cascades that promote mitochondrial remodeling.[3][10] These acute stresses, when applied repeatedly through training, produce cumulative adaptations that enhance mitochondrial content, improve mitochondrial quality, and optimize metabolic function. The magnitude and pattern of these metabolic perturbations determine the adaptive response. High-intensity exercise produces more pronounced metabolic stress, activating mitochondrial biogenesis pathways more robustly than work-matched moderate-intensity exercise.[21] Work-matched low-volume high-intensity exercise protocols produce greater metabolic perturbations, resulting in larger changes in muscle lactate and pH, and elicit more robust mitochondrial biogenic responses. Notably, only high-intensity exercise generating severe metabolic stress can compensate for reduced exercise volume, inducing mitochondrial biogenic mRNA responses comparable to those of high-volume moderate-intensity exercise.[21] However, the relationship between exercise intensity, volume, and mitochondrial adaptation is complex, with both high-intensity interval training and traditional endurance training producing substantial mitochondrial benefits through partially distinct mechanisms.[1][2][22] Recent evidence demonstrates that different exercise modalities induce distinct mitochondrial adaptation patterns in skeletal muscle, reflected in different network remodeling and molecular pathways.[22]

1.3 Bridging Sports Science and Preventive Medicine

The convergence of sports science and preventive medicine occurs at the level of mitochondrial adaptation. Training principles developed to enhance athletic performance such as periodization, progressive overload, specificity, and recovery, apply equally to exercise prescription for disease prevention and treatment. Understanding the molecular mechanisms of exercise-induced mitochondrial adaptation allows for evidence-based, precision exercise prescription tailored to specific clinical populations and therapeutic goals.[5][20] The most recent WHO 2020 guidelines on physical activity recommend that adults perform at least 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise per week, with muscle-strengthening activities on two or more days per week.[23] These guidelines, for the first time, include recommendations on sedentary behavior and specific guidance for people living with chronic diseases, reflecting the growing recognition of exercise as medicine.[23] As a safe and sustainable non-pharmacological intervention, regular exercise systematically remodels MQC structure and function by integrating signaling axes such as AMPK, SIRT1, and p38 MAPK, thereby promoting coordinated mitochondrial renewal and partially reversing aging-associated mitochondrial dysfunction.[5] The benefits of regular physical activity relate to delaying and reversing the onset of aging and age-related disorders, including cardiomyopathy, neurodegenerative diseases, cancer, obesity, diabetes, and fatty liver diseases, largely through improvements in mitochondrial dysfunction.[7]

2. Aim

The primary aim of this review is to comprehensively examine mitochondrial adaptations to exercise training and their role as a mechanistic bridge between sports science and preventive medicine, with focus on mitochondrial adaptations induced by different exercise modalities, molecular mechanisms regulating exercise-induced mitochondrial biogenesis, dynamics, and quality control. Additionally, this review explores relationship between mitochondrial adaptations and disease prevention, particularly for type 2 diabetes, cardiovascular disease, neurodegenerative disorders, and aging as well as, key regulatory pathways and therapeutic targets for optimizing mitochondrial health through exercise.

3. Materials and Methods

A comprehensive literature review was conducted to synthesize current evidence and clinical perspective on exercise-induced mitochondrial adaptations and their translational relevance to preventive medicine. Relevant articles were retrieved from electronic databases, including PubMed, Web of Science, and SPORTDiscus. The search covered publications from 2019 to 2026. The following keywords and their combinations were used: "mitochondrial biogenesis," "mitochondrial dynamics," "mitophagy," "mitochondrial quality control," "exercise training," "high-intensity interval training," "endurance training," "resistance training," "sprint interval training," "PGC-1α," "AMPK," "oxidative phosphorylation," "insulin resistance," "type 2 diabetes," "cardiovascular disease," "neurodegeneration," "aging," "sarcopenia," and "preventive medicine." Additional relevant studies were identified through manual screening of reference lists of selected articles. Inclusion criteria comprised full-text articles published in English, including systematic reviews, meta-analyses, randomized controlled trials, observational studies, mechanistic investigations, and narrative or other review articles addressing mitochondrial adaptations to exercise or their implications for chronic disease prevention. Particular emphasis was placed on recent high-quality evidence, including systematic reviews with meta-analyses and randomized controlled trials examining mitochondrial outcomes. Studies focusing exclusively on pharmacological interventions without an exercise component, articles published in languages other than English or without accessible full text, non-human studies lacking translational relevance, conference abstracts without full-text availability, and duplicate records were excluded. Titles and abstracts were screened for relevance, followed by full-text assessment of eligible studies. The final selection included studies evaluating or discussing mitochondrial biogenesis, dynamics, and quality control in response to exercise; molecular signaling pathways mediating mitochondrial adaptations; the role of mitochondrial dysfunction in metabolic, cardiovascular, and neurodegenerative diseases; comparative effectiveness of different exercise modalities on mitochondrial outcomes; and the translational potential of exercise-induced mitochondrial adaptations for disease prevention. The included studies were analyzed qualitatively and findings were synthesized descriptively to provide an overview of current evidence linking sports science and preventive medicine through mitochondrial biology, as well as to identify key clinical implications and research gaps.

4. Results

4.1 Mitochondrial Adaptations to Different Exercise Modalities

4.1.1 Comparative Effects: Endurance, HIIT, and Sprint Interval Training

A landmark 2025 systematic review and meta-regression analyzing 353 studies with 5,973 participants provided comprehensive evidence on mitochondrial and capillary adaptations to different exercise modalities.[1] After adjusting for relevant covariates including training frequency, intervention duration, and initial fitness level, percentage increases in mitochondrial content were similar across modalities: endurance training (ET) 23±5%, high-intensity interval training (HIT) 27±5%, and sprint interval training (SIT) 27±7% ($P>0.138$).[1] Critically, these adaptations were not influenced by age, sex, menopause, disease status, or the amount of muscle mass engaged, demonstrating the universality of mitochondrial adaptation to exercise.[1] The ability to adapt to exercise training is maintained throughout life, irrespective of sex and presence of disease, supporting exercise as a foundational intervention for preventive medicine applicable to diverse populations.[1]

However, substantial differences emerged in time efficiency. Per total hour of exercise, SIT was approximately 2.3 times more efficient in increasing mitochondrial content than HIT and 3.9 times more efficient than ET, while HIT was 1.7 times more efficient than ET.[1] Higher training frequencies (6>4>2

sessions/week) were associated with larger increases in mitochondrial content and VO_2max.[1] SIT was particularly effective in improving mitochondrial content and VO_2max in the early stages of training, while ET and HIT showed slower but steady improvements over a greater number of training weeks.[1] Capillaries per fiber increased similarly with ET (15±3%), HIT (13±4%), and SIT (10±11%) after adjustments.[1] However, capillaries per mm² only increased after ET (13±3%) and HIT (7±4%), with increases being larger after ET compared with HIT and SIT ($P<0.05$).[1]

A 2026 meta-analysis specifically examining moderate-intensity continuous training (MICT) in 14 studies (n=184) confirmed that MICT significantly increases mitochondrial volume density ($p<0.00001$), VO_2max ($p<0.0001$), citrate synthase activity ($p=0.05$), and mitofusin 2 (MFN2) expression ($p=0.01$).[24] However, no changes were observed for TFAM, DRP1, or PGC-1α, suggesting modality-specific molecular responses.[24]

4.1.2 High-Intensity Interval Training: Unique Mitochondrial Dynamics

HIIT induces unique mitochondrial structural and functional adaptations beyond simple increases in content. A 2023 randomized controlled trial comparing 12 weeks of supervised HIIT, resistance training (RT), and combined training (CT) revealed modality-specific mitochondrial remodeling.[2] Transmission electron microscopy demonstrated that HIIT increased mitochondrial volume, number, and perimeter ($P<0.01$), creating larger, more fused mitochondrial networks.[2] The molecular signature of HIIT included increased expression of OPA1 (a fusion protein) and decreased FIS1 (a fission protein), resulting in an elevated OPA1/FIS1 ratio indicative of enhanced mitochondrial fusion.[2] This fusion-favoring phenotype positively correlated with improvements in respiration ($r=0.69$, $P<0.05$), insulin sensitivity ($r=0.61$, $P<0.05$), and VO_2peak ($r=0.64$, $P<0.05$).[2] A 2025 study comparing HIIT and MICT effects on mitochondrial dynamics in 20 young males confirmed these findings, demonstrating that six weeks of training induced distinct remodeling of the mitochondrial network within skeletal muscle.[22] HIIT resulted in a stronger longitudinally oriented network with more pronounced increases in fusion protein expression and decreases in fission protein expression compared to MICT.[22] A 2025 study in high-fat diet fed rats demonstrated that 10 weeks of HIIT increased expression of PGC-1α, MFN2, and OPA1 genes while decreasing DRP1 and FIS1 genes, counteracting the negative effects of high-fat diet on mitochondrial function.[25]

4.1.3 Sprint Interval Training: Mitochondrial Stress Response and Supercomplex Assembly

A 2025 randomized controlled trial revealed that sprint-interval exercise (SIE) induces a unique mitochondrial stress signature and unfolded protein response (UPRmt).[26] Following 8 weeks of training, MICT increased mitochondrial content, complex I activity, and displayed enrichment of TCA cycle and OXPHOS proteins, while SIT improved respiratory function and upregulated pathways involved in 1-carbon metabolism and protein quality control.[26] Notably, COX7A2L was identified accumulating in III_2+IV_1 supercomplexes only after SIT.[26] Exercise-induced supercomplex formation represents a novel adaptive mechanism. A 2017 study provided the first evidence that exercise affects the stoichiometry of supercomplex formation in humans, with 4 months of exercise training increasing overall supercomplex content and redistributing complexes I, III, and IV to supercomplexes in the form of I+III+IV in older adults.[27] A 2022 study demonstrated that HIIT, compared with MICT, more effectively promoted mitochondrial supercomplex formation in aged female rats, accompanied by greater activation of the AMPK pathway and increased SOD2 protein levels.[28] A 2026 study further revealed that exercise induces sex-specific assembly of mitochondrial supercomplexes, with males increasing the assembly of complex III into supercomplexes in an intensity-dependent manner, while females showed stable supercomplex content during exercise.[29]

4.1.4 Resistance Training and Concurrent Training

A 2024 review examining the integrative effects of resistance training and endurance training on mitochondrial remodeling challenged the conventional view that resistance training-induced hypertrophy signaling interferes with endurance training-induced mitochondrial remodeling.[30] The review found that the resistance training component does not reduce muscle mitochondrial remodeling signals in concurrent training; on the contrary, concurrent training has the potential to amplify skeletal muscle mitochondrial biogenesis compared to a single exercise model.[30]

4.1.5 Rapid Mitochondrial Adaptations to Short-Term HIIT

Remarkably, mitochondrial adaptations to HIIT occur rapidly. A 2023 study demonstrated that just two weeks (seven sessions) of HIIT increases skeletal muscle mitochondrial respiration per mitochondrial protein by 18-24% for various substrates, indicating improved mitochondrial quality independent of content changes.[7] HIIT increased respiration per mitochondrial protein for lipid (+23%), complex I (+18%), complex I+II (+14%), and complex II (+24%).[7] These findings demonstrate that an early feature of aerobic training is increased mitochondrial protein quality via improved respiration and induction of mitochondrial transcriptional patterns.[7]

4.2 Molecular Mechanisms of Exercise-Induced Mitochondrial Adaptation

4.2.1 PGC-1α: The Master Regulator

PGC-1α functions as the master regulator of mitochondrial biogenesis, coordinating nuclear and mitochondrial gene expression.[31][32] A 2020 review highlighted that PGC-1α regulates not only mitochondrial biogenesis, but also mitochondrial quality control mechanisms including fission, fusion, and mitophagy.[31] Exercise induces significant increases in gene transcripts of various mitochondrial and autophagy-related genes in wild-type animals, but these responses are attenuated in PGC-1α knockout animals, which exhibit a 40% decrease in mitochondrial content and a 25% decline in running performance.[32]

4.2.2 AMPK Signaling and Mitochondrial Quality Control

AMPK serves as a cellular energy sensor that responds to increased AMP:ATP ratios during exercise. A 2017 study demonstrated that acute treadmill running causes mitochondrial oxidative stress and mitophagy post-exercise, preceded by increased phosphorylation of AMPK and ULK1, with ULK1 activation dependent on AMPK.[33] A 2021 study revealed that specific AMPK isoforms (α1/α2/β2/γ1) are localized on the outer mitochondrial membrane (mitoAMPK), and inhibition of mitoAMPK activity attenuates exercise-induced mitophagy in skeletal muscle in vivo.[34] Exercise preserves physical fitness during aging through AMPK and mitochondrial dynamics. A 2023 study using C. elegans demonstrated that daily exercise sessions delay the mitochondrial fragmentation and physical fitness decline that occur with aging, and that constitutive activation of AMPK uniquely preserves physical fitness during aging, a benefit abolished by impairment of mitochondrial fission or fusion.[35]

4.2.3 Mitochondrial Quality Control: An Integrated Network

MQC encompasses the coordinated processes of biogenesis, dynamics, and selective degradation (mitophagy) that maintain a healthy mitochondrial pool.[4][5] A 2022 review comprehensively described the regulatory networks coordinating MQC in skeletal muscle, emphasizing that in response to exercise, signaling to PGC-1α and other regulators produces an abundance of high-quality mitochondria, accompanied by an enhanced protein quality control system (UPRmt).[4] A 2026 review emphasized that MQC is a multitiered synergistic system, and that regular exercise systematically remodels its structure and function by integrating signaling axes such as AMPK, SIRT1, and p38 MAPK.[5]

4.2.4 Mitophagy: Exercise-Induced Selective Degradation

A 2020 review evaluated how ubiquitin-dependent mitophagy is regulated in muscle and non-muscle cells, finding that while PINK1-Parkin signaling is well-established in non-muscle cells, AMPK is emerging as a critical regulator of skeletal muscle mitophagy.[36] A 2022 study demonstrated that acute exercise rapidly activates hepatic mitophagic flux two hours post-exercise through both polyubiquitination and receptor-mediated pathways, demonstrating that exercise-induced mitochondrial quality control extends beyond skeletal muscle.[37]

4.2.5 Reactive Oxygen Species as Signaling Molecules

Exercise-induced ROS production is now recognized as an essential signaling mechanism for mitochondrial adaptation.[38][39] Moderate ROS levels generated during exercise activate redox-sensitive signaling pathways including AMPK, MAPK, NF-κB, and PGC-1α, driving adaptive responses.[38][39] Consistent with the principle of mitochondrial hormesis, moderate ROS exposure stimulates adaptive responses, while excessive ROS causes oxidative damage.[40] Importantly, antioxidant supplementation can blunt exercise-induced mitochondrial adaptations by preventing ROS-mediated signaling.[41]

4.3 Mitochondrial Adaptations and Disease Prevention

4.3.1 Type 2 Diabetes Mellitus

A comprehensive 2025 systematic review and meta-analysis of 18 studies (394 participants) examined the effects of exercise training on skeletal muscle mitochondrial outcomes in T2DM.[6] Exercise significantly enhanced mitochondrial oxidative capacity (SMD=0.61, 95% CI [0.30, 0.92]), mitochondrial antioxidant capacity (SMD=1.18, 95% CI [0.50, 1.86]), and the fusion marker MFN2 (SMD=0.96, 95% CI [0.63, 1.29]).[6] Effective modalities included long-term moderate aerobic training, short-term HIIT, and long-term resistance or combined training.[6] The American College of Sports Medicine 2022 consensus statement confirmed that regular training reduces HbA1c by 0.5-0.7% and improves insulin sensitivity, lipids, blood pressure, and fitness levels, even without weight loss.[42] A 2025 narrative review compared the molecular pathways through which ET and RT improve insulin resistance: RT enhances protein synthesis via the IGF-1/PI3K/AKT/mTOR pathway, while ET predominantly improves mitochondrial biogenesis and lipid oxidation through AMPK/SIRT1/PGC-1α signaling.[12]

4.3.2 Cardiovascular Disease

Exercise improves vascular health through mitochondrial adaptations. Aerobic exercise induces extensive mitochondrial adaptations through vascular mechanical stress and the increased production and release of ROS and nitric oxide that activate multiple intracellular signaling pathways, among which PGC-1α plays a critical role.[8] These adaptations improve bioenergetics, balance redox status, protect endothelial cells against detrimental insults, increase vascular plasticity, and ameliorate aging-related vascular dysfunction.[8]

Mitochondria serve as the central hub linking exercise to enhanced cardiac function.[16] Regular physical exercise mitigates sedentary-related cardiac damage and improves cardiac function, with exercise-induced improvements in mitochondrial function constituting a core mechanism underlying cardioprotective effects.[16] In heart failure, exercise training restores cardiac autophagic flux, which is associated with better mitochondrial quality control, bioenergetics, and cardiac function.[43] A 2023 study demonstrated that resistance training, particularly when combined with moderate-intensity continuous training (MRT), improved cardiac structure and function in heart failure mice through the HIF1α-Parkin-mitophagy pathway.[44] Exercise modality selection for heart failure should be etiology-specific: MICT may be the optimal modality for ischemic heart failure, while both MICT and HIIT (especially HIIT) are suitable for pressure-overload heart failure, with exercises differently improving myocardial autophagy through multiple mitophagy-related pathways.[45]

4.3.3 Neurodegenerative Diseases

Exercise-induced mitophagy represents a promising therapeutic strategy for Alzheimer's disease. A 2021 review confirmed that accumulating evidence shows beneficial effects of appropriate exercise on improved mitophagy and mitochondrial function to promote mitochondrial plasticity, reduce oxidative stress, enhance cognitive capacity, and reduce the risks of cognitive impairment and dementia in later life.[9] Stimulating mitophagy and optimizing mitochondrial function through exercise may forestall the neurodegenerative process of AD.[9] A 2023 study demonstrated that a 12-week treadmill exercise program improved mitochondrial function, decreased accumulation of β-amyloid plaques, and ameliorated loss of learning and memory ability by enhancing PINK1/Parkin-mediated mitophagy activity in the hippocampus of APP/PS1 mice.[46] The SIRT1-FOXO1/3 axis was identified as a key mediator through which exercise rescued PINK1/Parkin-mediated mitophagy.[46] A 2020 study confirmed that treadmill exercise attenuates Aβ-induced mitochondrial dysfunction and enhances mitophagy activity in APP/PS1 transgenic mice, restoring learning and memory ability while reversing mitochondrial dysfunction.[47]

A 2019 landmark study in Nature Neuroscience demonstrated that mitophagy stimulation through NAD+, urolithin A and actinonin supplementation reverses memory impairment in AD models through PINK1-, Parkin-, or DCT-1-dependent pathways, diminishes insoluble Aβ and prevents cognitive impairment, and abolishes AD-related tau hyperphosphorylation.[18] These findings suggest that impaired removal of defective mitochondria is a fundamental event in AD pathogenesis and that mitophagy represents a potential therapeutic intervention.[18]

4.3.4 Aging and Sarcopenia

A 2021 study in Nature Communications examined the impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function.[48] Aging was associated with a decline in mitochondrial capacity, exercise capacity and efficiency, gait stability, muscle function, and insulin sensitivity, even when maintaining an adequate daily physical activity level.[48] However, a further increase in physical activity level, achieved through regular exercise training, could largely negate the effects of aging.[48] Mitochondrial capacity correlated with exercise efficiency and insulin sensitivity, supporting a link between mitochondrial function and age-associated deterioration of skeletal muscle.[48] A 2023 study demonstrated that lifelong high-volume endurance exercise training increases mitochondrial volume and network connectivity in older human skeletal muscle, with highly trained older subjects exhibiting higher complex I+II-linked mitochondrial respiration per tissue mass than young untrained, older untrained, and older moderately trained subjects.[49] Furthermore, the protein content of ADP/ATP exchangers was higher and of the mitophagic marker parkin lower in highly trained older subjects, suggesting enhanced mitochondrial quality.[49]

A 2026 study in PNAS provided direct evidence that exercise-induced improvements in functional capacity, including reduced frailty in old mice, are dependent on mitochondrial adaptations in skeletal muscle at structural, enzymatic, and functional levels.[50] Skeletal muscle mitochondria maintain plasticity during aging in both mice and humans, and this preserved adaptability can be utilized to improve muscle performance and overall functional capacity.[50] Voluntary exercise also normalizes the proteomic landscape in muscle and brain and improves the phenotype of progeroid mice carrying mtDNA polymerase-γ mutations, significantly ameliorating premature aging phenotypes including decreased locomotor activity, alopecia, and kyphosis, while decreasing the mtDNA mutation load.[51]

4.3.5 Non-Alcoholic Fatty Liver Disease

Exercise training ameliorates NAFLD through mitochondrial mechanisms. Exercise increases PGC-1α expression, improves mitochondrial function, and leads to reduced hepatic steatosis, inflammation, fibrosis, and tumorigenesis.[52] A 2023 study demonstrated that exercise-induced hepatic Cdo1 expression activates the Camkk2-AMPK signaling pathway, promoting fatty acid oxidation and mitochondrial biogenesis in hepatocytes to attenuate hepatosteatosis.[53]A 2023 study revealed that aerobic exercise decreases the size of lipid droplets bound to mitochondria and the number of lipid droplet-mitochondria contacts in NAFLD models, with exercise increasing fatty acid oxidation in peridroplet mitochondria through a mitofusin-2-dependent mechanism.[54] A 2025 study confirmed that regular exercise alleviates metabolic dysfunction-associated steatohepatitis (MASH) through rescuing mitochondrial oxidative stress and dysfunction in the liver, enhancing mitochondrial quality control mechanisms including biogenesis, mitophagy, fusion, and fission.[55]

4.3.6 Cancer Prevention

Physical activity reduces the risk of colorectal, breast, lung, bladder, and gastric cancers by 10-20%, with studies showing a 40-50% reduction in cancer-specific mortality in breast, colorectal, and prostate cancers.[56] The concept of mitochondrial fitness emphasizes the crucial role of mitochondria in cell metabolism, particularly their oxidative functions, prevention of replication errors and regulation of apoptosis.[57] A 2022 study demonstrated that exercise induces metabolic reprogramming of internal organs by increasing nutrient demand and protects against metastatic colonization by limiting nutrient availability to the tumor, generating an exercise-induced metabolic shield. Exercise prior to cancer injection significantly protected against metastases in distant organs, with the protective effects dependent on mTOR activity.[58] A 2025 study confirmed that voluntary wheel running slows tumor growth and repartitions glucose uptake and oxidation to skeletal and cardiac muscle and away from tumors, suggesting that exercise-induced metabolic competition constrains tumor energetics.[59] Exercise also enhances antitumor immunity via activation of natural killer cells and CD8+ T lymphocytes, with exercise improving CD8+ T-cell antitumor efficacy through enhancing mitochondrial oxidative phosphorylation and increasing lactate-mediated stemness.[56][60]

4.4 Summary of Modality-Specific Mitochondrial Adaptations

The evidence reviewed demonstrates that different exercise modalities produce distinct but complementary mitochondrial adaptations.

Endurance Training (ET): Increases mitochondrial content (23±5%), capillarization (13±3% capillaries/mm²), citrate synthase activity, and MFN2 expression. Promotes grid-like mitochondrial network remodeling. Enriches TCA cycle and OXPHOS proteins. Most effective for capillary density improvements.[1][2][3]

High-Intensity Interval Training (HIIT): Increases mitochondrial content (27±5%), promotes mitochondrial fusion (increased OPA1, decreased FIS1), creates larger, more fused mitochondrial networks. Uniquely correlates with improved insulin sensitivity and VO_2peak. More effectively activates AMPK pathway and promotes supercomplex formation compared to MICT. Rapid quality improvements within 2 weeks.[4][5][6]

Sprint Interval Training (SIT): Increases mitochondrial content (27±7%), most time-efficient modality (3.9× more efficient than ET). Induces unique mitochondrial stress signature and UPRmt. Promotes COX7A2L accumulation in III_2+IV_1 supercomplexes. Upregulates 1-carbon metabolism and protein quality control pathways.[1][7][3]

Resistance Training (RT): Does not significantly increase mitochondrial abundance but optimizes mitochondrial quality and efficiency. Increases mitochondrial surface area and cristae density in strength athletes.[8] Does not interfere with endurance-induced mitochondrial remodeling in concurrent training; may amplify mitochondrial biogenesis signals.[9]

Concurrent Training (CT): Increases mitochondrial number without proportional increases in volume or perimeter. Has the potential to amplify skeletal muscle mitochondrial biogenesis compared to single-modality training. Differential sequencing of resistance and endurance components may result in varied mitochondrial biogenesis signals.[4][9]

4.5 Mitochondrial Adaptations Across Tissues

Exercise-induced mitochondrial adaptations extend beyond skeletal muscle to multiple organ systems.

Vascular System: Aerobic exercise induces extensive mitochondrial adaptations through vascular mechanical stress and increased production of ROS and nitric oxide, activating PGC-1α-dependent pathways that improve bioenergetics, balance redox status, and ameliorate aging-related vascular dysfunction.[10]

Cardiac Muscle: Mitochondria serve as the central hub linking exercise to enhanced cardiac function. Exercise promotes intrinsic myocardial changes including increased cytosolic antioxidant capacity, altered mitochondrial phenotype, and myokine-mediated metabolic and anti-inflammatory effects.[11][12]

Liver: Exercise rapidly activates hepatic mitophagic flux and promotes fatty acid oxidation through the Cdo1-Camkk2-AMPK signaling pathway, attenuating hepatosteatosis.[13][14] Exercise also modifies lipid droplet-mitochondria communication through a mitofusin-2-dependent mechanism.[15]

Brain: Exercise enhances PINK1/Parkin-mediated mitophagy in the hippocampus, improving mitochondrial function, decreasing β-amyloid plaque accumulation, and ameliorating cognitive decline in AD models.[16][17]

5. Discussion

5.1 Mitochondrial Health as a Unifying Therapeutic Target

The evidence synthesized in this review demonstrates that mitochondrial adaptations represent a fundamental mechanism linking exercise training to disease prevention across multiple organ systems and disease states. Mitochondrial dysfunction is a common pathophysiological feature of T2DM, cardiovascular disease, neurodegenerative disorders, NAFLD, cancer, and age-related decline.[9][18] Exercise training, through coordinated improvements in mitochondrial biogenesis, dynamics, quality control, and respiratory function, addresses this shared pathophysiology, positioning mitochondrial health as a unifying therapeutic target bridging sports science and preventive medicine.

The landmark finding that mitochondrial adaptations to exercise are preserved across age, sex, and disease status has profound implications for preventive medicine.[1] Exercise-based interventions targeting mitochondrial health can be applied across the lifespan and across clinical populations, from healthy athletes seeking performance optimization to elderly patients with chronic disease seeking functional improvement.

5.2 Precision Exercise Prescription Based on Mitochondrial Targets

The modality-specific mitochondrial adaptations identified in this review provide a scientific foundation for precision exercise prescription. For patients with insulin resistance or T2DM, HIIT may be particularly beneficial given its unique ability to promote mitochondrial fusion and its strong correlation with improved insulin sensitivity.[4][19] For patients with limited time availability, SIT offers the most time-efficient approach to increasing mitochondrial content.[1] For patients with cardiovascular disease, endurance training provides the greatest capillarization benefits, while HIIT more effectively promotes supercomplex formation and AMPK activation.[1][6][20] The rapid time course of mitochondrial adaptation with quality improvements evident within 2 weeks of HIIT, has important clinical implications, suggesting that meaningful mitochondrial improvements can occur early in a training program, potentially enhancing patient motivation and adherence.[5]

5.3 Molecular Mechanisms: From Acute Signaling to Chronic Adaptation

The molecular mechanisms governing exercise-induced mitochondrial adaptation involve a sophisticated interplay of signaling pathways. The AMPK-PGC-1α axis serves as the central regulatory hub, with AMPK sensing energetic stress and activating PGC-1α to coordinate mitochondrial biogenesis.[21][22] The discovery of mitochondria-localized AMPK (mitoAMPK) adds spatial specificity to this signaling, allowing targeted quality control of individual mitochondria within the network.[23] Exercise-induced ROS production, operating through the hormesis principle, activates redox-sensitive signaling pathways that drive adaptive responses.[24][25] The finding that antioxidant supplementation can blunt exercise-induced mitochondrial adaptations underscores the importance of ROS as essential signaling molecules rather than merely damaging byproducts.[26] Mitochondrial quality control operates as an integrated network encompassing biogenesis, dynamics (fission/fusion), mitophagy, and the mitochondrial unfolded protein response.[27][28] Exercise coordinates these processes to maintain a healthy mitochondrial pool, with the balance between these processes determining the net mitochondrial phenotype. The exercise-induced mitochondrial dynamics cycle, characterized by fragmentation during exercise followed by fusion during recovery, represents a fundamental mechanism for mitochondrial renewal.[29]

5.4 Clinical Translation: From Bench to Bedside

The translation of mitochondrial biology into clinical practice requires consideration of several factors. First, exercise prescription should be individualized based on the patient's clinical condition, fitness level, and therapeutic goals. The WHO 2020 guidelines provide a framework, recommending 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise per week, with muscle-strengthening activities on two or more days per week.[30][31] Second, the concept of "mitochondrial fitness" extends beyond traditional fitness metrics. Mitochondrial health encompasses not only content and respiratory capacity but also dynamics, quality control, and supercomplex assembly.[32][20] Future clinical assessment tools may incorporate mitochondrial biomarkers to guide exercise prescription and monitor therapeutic response. Third, exercise-induced mitochondrial adaptations may synergize with pharmacological interventions. For example, mitophagy-enhancing compounds (NAD+ precursors, urolithin A) have shown promise in preclinical AD models, and exercise may potentiate these effects through complementary mechanisms.[33] Similarly, exercise may enhance the efficacy of cancer immunotherapies by improving CD8+ T-cell mitochondrial function.[34]

5.5 Limitations and Future Directions

Several limitations should be acknowledged. First, many mechanistic studies rely on animal models, and translation to human physiology requires caution. Second, the optimal dose-response relationship between exercise and mitochondrial adaptation remains incompletely defined, particularly for clinical populations. Third, most studies examine skeletal muscle, and the mitochondrial adaptations in other tissues (brain, liver, vasculature) are less well characterized in humans. Fourth, inter-individual variability in mitochondrial response to exercise is substantial and poorly understood. Future research should focus on: (1) defining optimal exercise prescriptions for specific mitochondrial targets in different clinical populations; (2) developing non-invasive biomarkers of mitochondrial health for clinical monitoring; (3) investigating the interaction between exercise-induced mitochondrial adaptations and pharmacological interventions; (4) elucidating sex-specific differences in mitochondrial adaptation, particularly regarding supercomplex assembly; and (5) exploring the role of exercise in modulating mitochondrial-organelle communication and inter-organ crosstalk.[35]

6. Conclussions

Exercise-induced mitochondrial adaptations represent a fundamental mechanistic bridge between sports science and preventive medicine.

1. **Universal adaptability:** Mitochondrial adaptations to exercise training are preserved across age, sex, and disease status, supporting exercise as a foundational intervention for all populations.[1]

2. **Modality-specific responses:** Different exercise modalities produce distinct but complementary mitochondrial adaptations. HIIT uniquely promotes mitochondrial fusion and correlates with improved insulin sensitivity; SIT is the most time-efficient for increasing mitochondrial content; ET provides the greatest capillarization benefits; and RT optimizes mitochondrial quality without proportional content increases.[1][4][7]

3. **Rapid adaptation:** Meaningful mitochondrial quality improvements occur within 2 weeks of HIIT, with content increases developing over longer training periods.[5]

4. **Integrated molecular regulation:** Exercise-induced mitochondrial adaptation is governed by coordinated signaling through AMPK, PGC-1α, and mitochondrial quality control pathways, with spatial specificity provided by mitoAMPK.[21][23][22]

5. **Multi-organ benefits:** Exercise-induced mitochondrial adaptations extend beyond skeletal muscle to vascular, cardiac, hepatic, and neural tissues, providing systemic protection against chronic disease.[10][16][15][14]

6. **Disease prevention:** Exercise-induced mitochondrial improvements directly address the mitochondrial dysfunction underlying T2DM, cardiovascular disease, neurodegenerative disorders, NAFLD, cancer, and age-related decline.[19][11][16][15][36]

7. **Therapeutic synergy:** Exercise-induced mitochondrial adaptations may synergize with pharmacological interventions, including mitophagy enhancers and cancer immunotherapies, opening new avenues for combination therapy.[33][34]

Mitochondrial health emerges as a unifying therapeutic target that bridges the traditionally separate disciplines of sports science and preventive medicine. Understanding the molecular mechanisms of exercise-induced mitochondrial adaptation provides a scientific foundation for precision exercise prescription, enabling clinicians to tailor exercise interventions to specific mitochondrial targets and clinical goals. As the global burden of chronic disease continues to rise, leveraging exercise-induced mitochondrial adaptations represents a cost-effective, evidence-based strategy for disease prevention and health promotion across the lifespan.

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