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The Role of Mitochondrial Dynamics in Metabolic Dysfunction-Associated Steatotic Liver Disease and Regulatory Mechanisms of Exercise Intervention: A Systematic Review

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 November 2025 and was last updated on 29 November 2025.

INTRODUCTION

Review question / Objective Main Objective: The primary objective of this systematic review is to synthesize existing evidence from animal studies to evaluate the regulatory effects of exercise interventions on hepatic mitochondrial dynamics in the context of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Specifically, this review aims to clarify how different exercise modalities modulate key proteins involved in mitochondrial fusion and fission, thereby remodeling the hepatic mitochondrial network.
Specific Questions:
1. How does MASLD pathology alter the expression of hepatic mitochondrial dynamics markers, specifically fusion proteins and fission proteins ?
2. Can chronic exercise intervention reverse the dysregulated mitochondrial dynamics observed in MASLD?
3. Is there a difference in efficacy between different exercise intensities or modalities in remodeling mitochondrial dynamics?
4. Does the efficacy of exercise on mitochondrial dynamics vary depending on the disease stage (simple steatosis vs. MASH) or etiology?

Condition being studied Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as Non-Alcoholic Fatty Liver Disease (NAFLD), is a chronic liver condition characterized by the accumulation of excess fat in the liver in the presence of metabolic dysfunction. It was renamed following a 2023 multi-society consensus to better reflect its pathophysiology. MASLD is highly prevalent, affecting approximately 32.4% of the global population, and is closely linked to obesity, type 2 diabetes, and other metabolic disturbances.
The clinical spectrum of MASLD ranges from simple steatosis (MAFL) to Metabolic Dysfunction-Associated Steatohepatitis (MASH), which is

marked by inflammation and hepatocyte injury. This can progressively worsen to fibrosis, cirrhosis, and ultimately hepatocellular carcinoma. The pathogenesis is complex, involving a "multiple-hit" mechanism. Crucially, recent evidence highlights that dysregulated mitochondrial dynamics—specifically the disruption of the equilibrium between mitochondrial fusion and fission—are pivotal in driving the onset and progression of the disease by impairing cellular energy metabolism and inducing oxidative stress.

METHODS

Search strategy Electronic Databases: A comprehensive literature search was conducted in PubMed and Web of Science databases to identify relevant studies investigating the effects of exercise on mitochondrial dynamics in MASLD.
Search Terms: The search strategy was constructed based on the PICOS principle using a combination of Medical Subject Headings (MeSH) and free-text terms. Boolean operators (AND, OR, NOT) were utilized to combine the following search strings:
Disease Terms: ("Metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "Metabolic dysfunction-associated fatty liver disease" OR "MAFLD" OR "Non-alcoholic Fatty Liver Disease" OR "NAFLD" OR "Nonalcoholic Steatohepatitis" OR "NASH" OR "Fatty Liver" OR "Hepatic Steatosis" OR "Diet, High-Fat").
Mechanism Terms: AND ("Mitochondrial dynamics" OR "Mitochondrial fission" OR "Mitochondrial fusion" OR "Mitochondrial biogenesis" OR "Mitochondrial quality control" OR "Drp1" OR "Mfn1" OR "Mfn2" OR "Mitofusin" OR "OPA1" OR "Fis1" OR "MFF").
Intervention Terms: AND ("Exercise" OR "Physical Activity" OR "Training" OR "Running" OR "Swimming" OR "Treadmill" OR "Aerobic" OR "Resistance training" OR "HIIT" OR "High-intensity interval training" OR "MICT" OR "Moderate-intensity continuous training").
Filters and Limits:
Language: The search was restricted to articles published in English.
Publication Type: Reviews, systematic reviews, and meta-analyses were excluded using the NOT boolean operator (e.g., NOT "Review"[Publication Type]) or during the screening process.
Species: No search filters were applied to restrict the species (e.g., excluding humans) in the initial database search to ensure comprehensiveness. However, during the screening process, only animal studies were identified that met the inclusion criteria, as no human clinical trials investigating these specific hepatic mitochondrial dynamics markers were retrieved.
Search Date: The search includes all records available in the databases up to the date of the final search execution.

Participant or population This review addresses animal models with experimentally induced Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) or Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD).
Specific inclusion criteria for participants are:
Species: Rodents (mice and rats) and zebrafish.
Disease State: Animals exhibiting any stage of the disease spectrum, including simple steatosis (MAFL) and Metabolic Dysfunction-Associated Steatohepatitis (MASH).
Induction Methods: Models induced by various protocols, including but not limited to:
Dietary interventions (e.g., High-Fat Diet, Methionine-Choline Deficient diet, High-Fat High-Sucrose diet).
Pharmacological induction (e.g., Dexamethasone).
Comorbidity models (e.g., MASLD combined with Type 2 Diabetes Mellitus or Gestational Diabetes Mellitus).
Exclusion: Studies involving healthy animals without disease induction.

Intervention The review evaluates chronic physical exercise training protocols utilized as therapeutic interventions. The specific interventions included are:
Aerobic Exercise: This encompasses various modalities such as treadmill running and swimming. The review specifically categorizes and evaluates these based on intensity, including Moderate-Intensity Continuous Training (MICT), High-Intensity Interval Training (HIIT), and Voluntary Wheel Running (VWR).
Resistance Exercise: Training protocols designed to increase muscle strength, such as ladder climbing models.
Combined Training: Protocols that integrate both aerobic and resistance training components.
The review includes interventions of any frequency or duration, provided they constitute a chronic training regimen. Single-bout (acute) exercise protocols were explicitly excluded from the evaluation.

Comparator The primary comparator consists of sedentary control groups. These are animals with the same induced disease condition (MASLD/MAFLD) that did not undergo any exercise intervention, serving as a baseline to evaluate the effects of exercise.

Additionally, where available, the review compares different exercise intervention groups against each other to evaluate the relative efficacy of different exercise intensities and modalities on mitochondrial dynamics.

Study designs to be included This review includes original controlled experimental animal studies (in vivo). Eligible studies utilized randomized or non-randomized designs comparing chronic exercise interventions against sedentary controls in induced MASLD/MAFLD animal models (rodents or zebrafish). Acute exercise studies, in vitro studies, reviews, and studies lacking a disease control group were excluded.

Eligibility criteria In addition to the PICOS criteria, the following eligibility criteria were applied:
Language: Only articles published in English were included.
Publication Type: The review included full-text original research articles. Conference abstracts, editorials, reviews, systematic reviews, and meta-analyses were excluded. Studies where the full text was unavailable were also excluded.
Tissue Specificity: Studies were required to analyze liver tissue. Studies investigating mitochondrial dynamics in other tissues (e.g., skeletal muscle) without hepatic data were excluded.
Outcome Measurement: Eligible studies must provide objective quantitative measurements (e.g., Western Blot, RT-qPCR) of the target proteins or genes. Studies relying exclusively on subjective qualitative analysis (e.g., electron microscopy images without quantification) were excluded. Furthermore, studies reporting only phosphorylated forms of markers (e.g., p-Drp1) without reporting total protein levels were excluded.

Information sources PubMed and Web of Science.

Main outcome(s) The primary outcome of the review is the quantitative alteration in the expression of key markers regulating hepatic mitochondrial dynamics following exercise intervention.
Specific markers analyzed include:
Mitochondrial Fusion Markers: Mitofusin 1 (MFN1), Mitofusin 2 (MFN2), and Optic Atrophy 1 (OPA1).
Mitochondrial Fission Markers: Dynamin-related protein 1 (Drp1) and Fission protein 1 (Fis1).
Effect Measures: Outcomes are evaluated based on objective quantitative data reported in the included studies. The primary measures are protein abundance levels assessed via Western Blotting and gene expression (mRNA) levels assessed via RT-qPCR.
Timing: Outcomes are measured at the endpoint of the study (post-intervention), which typically ranges from 4 to 12 weeks in duration depending on the specific study design.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included animal studies were assessed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool. This tool is specifically designed for animal intervention studies.
Two reviewers independently evaluated the risk of bias for each included study. The assessment covered domains such as selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Any discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer. No studies were excluded based on the quality assessment scores; instead, the assessment results were used to interpret the findings and evaluate the overall strength of the evidence.

Strategy of data synthesis A narrative synthesis of the findings will be performed. Due to the significant heterogeneity in animal models (species, strains), disease induction protocols (e.g., high-fat diet vs. methionine-choline deficient diet vs. drug induction), and exercise interventions (varying modalities, intensities, and durations), a quantitative meta-analysis is not appropriate.
The data will be synthesized and structured according to the following categories:
Disease Stage: Sub-grouping studies by simple steatosis (MAFL) versus steatohepatitis (MASH).
Intervention Modality: Comparing outcomes across different exercise types (MICT, HIIT, Resistance Training).
Results will be presented in text and summary tables (e.g., Table 1), highlighting the direction of statistically significant changes (upregulation, downregulation, or no change) in mitochondrial dynamics markers (MFN1/2, OPA1, Drp1, Fis1) relative to sedentary controls.

Subgroup analysis Based on the narrative synthesis approach, the included studies were stratified and analyzed according to the following subgroups:
Disease Model/Stage: Results were analyzed separately for models of simple steatosis (MAFL) versus steatohepatitis (MASH) versus drug-induced/comorbidity models to determine if

disease severity or etiology influences the efficacy of exercise.
Exercise Modality and Intensity: Interventions were categorized to compare the effects of different intensities (e.g., Voluntary Wheel Running [VWR] vs. Forced Aerobic Exercise) and modalities (Moderate-Intensity Continuous Training [MICT] vs. High-Intensity Interval Training [HIIT]) on mitochondrial dynamics markers.

Sensitivity analysis Not applicable. A quantitative meta-analysis was not conducted due to the significant heterogeneity in animal species, disease induction protocols, and exercise regimens among the included studies. Consequently, no statistical sensitivity analysis was performed.

Country(ies) involved China.

Keywords exercise; mitochondrial dynamics; MASLD.

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