Hepatic Macrophage Polarization: A New Target for Exercise in the Prevention and Treatment of Non-alcoholic Fatty Liver Disease (Postprint)

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Abstract

The efficacy of exercise in the prevention and treatment of non-alcoholic fatty liver disease (NAFLD) has been widely recognized, yet mechanistic research has yet to achieve breakthrough progress. The polarization status of hepatic macrophages is closely associated with the onset and progression of NAFLD, but research findings lack effective integration. This article further analyzes the effects of exercise on macrophage polarization and its therapeutic efficacy against NAFLD based on dissecting the relationship between hepatic macrophage polarization and various stages of NAFLD. The results demonstrate that under normal conditions, resident hepatic Kupffer macrophages maintain a dynamic equilibrium between pro-inflammatory M1 and anti-inflammatory M2 phenotypes; during the early stage of NAFLD, aerobic exercise of varying intensities can suppress the elevation of the M1/M2 ratio by inhibiting either the infiltration of exogenous macrophages or the polarization of Kupffer cells toward the M1 phenotype, thereby exerting significant preventive effects in early NAFLD; subsequently, hepatic macrophages gradually exhibit increased stress-induced M2 polarization, which at this stage primarily functions to promote the activation of hepatic stellate cells and the differentiation of extracellular matrix, leading to hepatic fibrosis and even cirrhosis and hepatocellular carcinoma. In summary, this study suggests that macrophage polarization may represent a novel target for exercise-based prevention and treatment of NAFLD; blocking the infiltration of exogenous macrophages or inhibiting the polarization of Kupffer cells toward the M1 phenotype constitutes an important strategy for preventing NAFLD progression; whereas when the disease advances to the stages of fibrosis, cirrhosis, or hepatocellular carcinoma, preventing stress-induced polarization of macrophages toward the M2 phenotype may serve as an effective therapeutic target.

Full Text

Liver Macrophage Polarisation: A New Target for Exercise Prevention and Treatment of Non-alcoholic Fatty Liver Disease

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Abstract

The efficacy of exercise in preventing and treating non-alcoholic fatty liver disease (NAFLD) is widely recognized, yet mechanistic insights remain limited. Hepatic macrophage polarization is intimately associated with NAFLD pathogenesis, but research findings lack effective integration. This review analyzes the relationship between liver macrophage polarization and NAFLD progression, and further examines how exercise influences macrophage polarization and its therapeutic effects on NAFLD. Under physiological conditions, resident Kupffer macrophages maintain dynamic equilibrium between pro-inflammatory M1 and anti-inflammatory M2 phenotypes. In early-stage NAFLD, aerobic exercise of varying intensities can inhibit the elevation of the M1/M2 ratio by suppressing either exogenous macrophage infiltration or Kupffer cell polarization toward the M1 phenotype, demonstrating significant preventive and therapeutic effects. As the disease progresses, liver macrophages exhibit increased stress-induced M2 polarization, which primarily promotes hepatic stellate cell activation and extracellular matrix differentiation, leading to fibrosis, cirrhosis, and even hepatocellular carcinoma. In summary, macrophage polarization may represent a novel target for exercise-based NAFLD prevention and treatment. Blocking exogenous macrophage infiltration or inhibiting M1 polarization of Kupffer cells constitutes an important strategy for preventing NAFLD progression. However, when the disease advances to fibrosis, cirrhosis, or hepatocellular carcinoma stages, preventing stress-induced M2 polarization of macrophages may be an effective therapeutic target.

Keywords: Non-alcoholic fatty liver disease; Metabolic associated fatty liver disease; Kupffer cells; Macrophage polarization; Exercise; Inflammatory reaction

1. Literature Search Strategy

We systematically searched PubMed, China National Knowledge Infrastructure (CNKI), and other databases from inception to July 2024. Chinese search terms included "non-alcoholic fatty liver disease," "metabolic associated fatty liver disease," "non-alcoholic fatty liver," "non-alcoholic steatohepatitis," "hepatic fibrosis," "macrophages," and "exercise," using multiple search strategies targeting titles, abstracts, and keywords. English search terms included "nonalcoholic fatty liver disease," "metabolic associated fatty liver disease," "nonalcoholic fatty liver," "nonalcoholic steatohepatitis," "hepatic fibrosis," "macrophages," and "exercise," with multiple search strategies applied to "Title/Abstract." Literature quality was assessed using EndNote software. Inclusion criteria were: (1) high-quality studies published in Chinese or English; (2) studies related to macrophages and NAFLD; (3) studies related to exercise and NAFLD; (4) studies related to exercise and macrophages; (5) studies linking exercise, macrophages, and NAFLD; and (6) seminal works supporting our arguments. Exclusion criteria were: (1) duplicate or irrelevant studies; (2) outdated publications; and (3) studies without full-text availability. Ultimately, 5 Chinese and 77 English articles were included, totaling 82 references. The literature screening flowchart and search strategies are provided in the Appendix.

2.1 Overview of NAFLD

Nutrient excess leading to rapid weight gain and obesity, diabetes, and hyperlipidemia are primary risk factors for NAFLD. Since 2020, the term "metabolic associated fatty liver disease" (MAFLD) has been introduced to exclude viral and alcohol-related liver disease, though NAFLD remains widely used in most literature [5-6]. NAFLD progression encompasses three stages: early-stage simple non-alcoholic fatty liver (NAFL), characterized by excessive hepatic lipid deposition without significant liver dysfunction [7]; progression to non-alcoholic steatohepatitis (NASH), where hepatic fat accumulation triggers inflammatory responses and liver function abnormalities, with biopsy revealing steatosis, ballooning degeneration, and lobular inflammation [8-9]; and chronic inflammatory injury leading to hepatic stellate cell (HSC) activation and extracellular matrix (ECM) protein accumulation, gradually developing into hepatic fibrosis and potentially progressing to cirrhosis or hepatocellular carcinoma [10].

The prevalence of NAFLD in adults ranges from 10% to 30%, with 10% to 20% progressing to NASH, which carries a 25% risk of developing cirrhosis within 10 years. Regardless of stage, hepatic inflammation resulting from excessive lipid deposition represents the common pathological basis [11]. Hepatic macrophages are crucial for maintaining inflammatory homeostasis, and recent studies have identified triggering receptor expressed on myeloid cells 2 (TREM2) as a non-invasive biomarker for NASH diagnosis [12], avoiding the need for invasive liver biopsy. TREM2 is a macrophage surface receptor protein, and its high expres-

sion in NASH patients correlates strongly with hepatic steatosis, ballooning degeneration, and lobular inflammation [12], demonstrating that macrophages play a critical role in NAFLD pathogenesis.

2.2 Macrophage Subtypes and Characteristics in NAFLD

Hepatic macrophages exhibit tissue heterogeneity. Single-cell gene and protein sequencing analyses classify human hepatic macrophages into tissue-resident macrophages (Kupffer cells, KCs) expressing surface markers $CD11b^+$, $F4/80^+$, $TIM4^+$, and $CLEC4F^+$, and bone marrow-derived infiltrating macrophages expressing $CD11b^+$, $F4/80^+$, $CCR2^+$, and $CX3CR1^+$ [13-14]. Based on activation programs, macrophages can be categorized into classically activated pro-inflammatory M1 phenotype and alternatively activated anti-inflammatory M2 phenotype, which can interconvert under specific conditions [15-17]. In healthy mouse livers, hepatic macrophages consist primarily of KCs, comprising 20% to 25% of non-parenchymal cells [18]. KCs maintain inflammatory homeostasis by clearing apoptotic cells through efferocytosis and eliminating foreign pathogens [19-20].

Under obese conditions, hepatic lipid deposition triggers a dramatic increase in bone marrow-derived monocyte infiltration, which differentiate into macrophages surrounding hypertrophic adipocytes to form hepatic crown-like structures (hCLS) [21-22]. Multiple studies have detected lipid-associated macrophage (LAM) subtypes in NASH liver hCLS, characterized by high TREM2 expression [23-26], leading to the proposal of TREM2 as a non-invasive biomarker for NASH diagnosis [12].

In summary, hepatic macrophages comprise resident KCs and bone marrow-derived infiltrating macrophages. Under physiological conditions, KCs predominate and maintain inflammatory homeostasis while promoting tissue repair and regeneration. However, in NAFLD, pro-inflammatory M1 infiltrating macrophages increase dramatically, producing abundant pro-inflammatory cytokines and causing inflammatory dysregulation. The composition and phenotypic distribution of hepatic macrophages are closely related to NAFLD development and prognosis.

2.3.1 Early-Stage NAFLD Macrophage Polarization Characteristics

In early-stage NAFL, massive bone marrow-derived monocytes infiltrate the liver under C-C motif chemokine ligand 2 (CCL2) mediation and differentiate into macrophages predominantly exhibiting pro-inflammatory M1 characteristics, representing the primary cause of elevated M1/M2 ratios during this stage. Infiltrating macrophages exacerbate hepatic steatosis by promoting chemokine secretion and releasing inflammatory cytokines such as tumor necrosis factor-

α (TNF-α), interleukin (IL)-1β, and IL-6 [29-30]. Adipokines released from hepatic adipocytes, such as leptin and calprotectin (S100A8 and S100A9), can stimulate hepatic macrophages to release pro-inflammatory factors via toll-like receptor 4 (TLR4) and NLRP3 inflammasome signaling pathways, amplifying hepatic inflammation [31-32]. Without timely intervention, approximately 20% of NAFL cases progress to steatohepatitis [20].

In the NASH stage, persistent macrophage infiltration and increased M1 polarization of Kupffer cells collectively disrupt hepatic inflammatory homeostasis. Significantly increased chemokine expression is a key factor inducing macrophage infiltration; knockout of CCL2 or C-X3-C motif chemokine ligand 1 (CX3CL1) genes markedly suppresses macrophage infiltration in NASH mice [33-34]. Activation of p38α protein kinase [35], transmembrane glycoprotein CD44 [36], and TLR4 [37] signaling pathways participates in M1 polarization of Kupffer cells. Both in vivo and in vitro interventions demonstrate that annexin A5 (Anx A5) can reprogram macrophage metabolism from glycolysis to oxidative phosphorylation by targeting pyruvate kinase M2 (PKM2), thereby inducing M2 polarization and ameliorating steatosis, inflammation, and fibrosis in NASH mice [38]. Additionally, myeloid cell transcription factor forkhead box O1 (FOXO1) knockout induces M2 polarization of hepatic Kupffer cells, alleviating high-fat diet-induced hepatic inflammation [39].

These studies consistently demonstrate that in early NAFLD, the increased M1/M2 ratio primarily results from bone marrow-derived macrophage infiltration. As the disease progresses to NASH, persistent macrophage infiltration is accompanied by increased M1 polarization of Kupffer cells. Interventions targeting macrophage infiltration or blocking M1 polarization effectively delay NAFLD progression, providing a theoretical basis for therapeutic strategies.

2.3.2 Late-Stage NAFLD Macrophage Polarization Characteristics: Macrophage-Hepatic Stellate Cell Crosstalk Mediates Fibrosis Progression

In early hepatic fibrosis, Kupffer cells secrete abundant chemokines while performing efferocytosis of apoptotic cells, exacerbating exogenous macrophage infiltration. As infiltrating macrophages increase, cytokines such as transforming growth factor-β (TGF-β), IL-1β, and TNF-α rise dramatically, further activating HSCs and promoting fibrosis progression [40-45]. Using single-cell transcriptomics, Ren et al. [46] extracted three macrophage subclusters (Mac1, Mac2, and Mac3) from cirrhotic and hepatocellular carcinoma tissues, finding that only Mac1 originated from Kupffer cells while Mac2 and Mac3 derived from blood monocytes, with their numbers significantly increased in cirrhotic tissues, indicating persistent exogenous macrophage infiltration throughout NAFLD progression to cirrhosis and carcinoma.

Infiltrating macrophage LAM subtypes characterized by TREM2 expression are

particularly abundant in fibrotic regions, further demonstrating the importance of macrophage infiltration in hepatic fibrosis [47]. Studies using gene knockout or specific inhibitors consistently show that suppressing pro-inflammatory factors such as TGF-$ 1, $IL-1$, andTNF-$ [48-50] or inducing M2 macrophage polarization [51] effectively ameliorates early hepatic fibrosis.

However, recent studies have identified stress-induced M2 polarization increase in Kupffer cells during advanced cirrhosis and hepatocellular carcinoma stages. At this juncture, the anti-inflammatory effects of M2 macrophages are minimal; instead, they primarily promote extracellular matrix differentiation, HSC activation, and angiogenesis, contributing to cirrhosis and hepatocarcinogenesis [52]. Earlier studies demonstrated that chronic hepatitis C virus promotes HSC activation and fibrosis-cirrhosis by inducing Kupffer cell M2 polarization [10]. Recent findings show that late-stage fibrotic M2 macrophages enhance HSC autophagy by secreting prostaglandin E2 (PGE2) and binding to PGE2 receptors on HSCs, thereby augmenting HSC activity and exacerbating extracellular matrix deposition and fibrosis [53]. Mechanisms underlying M2 polarization remain understudied. Zhao et al. [54] found that exosomal miR-934 induces M2 polarization by activating phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB) signaling, accelerating colorectal cancer liver metastasis and worsening prognosis. In studies of endemic arsenicosis-induced hepatic fibrosis, arsenite was found to induce M2 polarization via miR-21 activation of mammalian target of rapamycin (mTOR) signaling and regulation of phosphatase and tensin homolog (PTEN), which participates in HSC activation, collagen synthesis, and fibrosis [55]. Although not directly focused on NAFLD, these studies partially explain potential mechanisms of hepatic macrophage M2 polarization.

Notably, tail vein injection of M1 bone marrow-derived macrophages (BMDMs) in fibrotic mice induced HSC apoptosis and hindered fibrosis progression, whereas M2 BMDM injection had no effect [51], further suggesting that M2 polarization in advanced fibrosis is detrimental to disease resolution. Additionally, anti-breast cancer drug development studies have shown that thymosin α-1 and BMS794833 (efferocytosis inhibitors) exhibit anti-cancer effects by inhibiting tumor macrophage M2 polarization [56-57], providing valuable insights for targeting macrophage polarization in advanced NAFLD.

In summary, during advanced NAFLD with fibrosis-cirrhosis and hepatocellular carcinoma, stress-induced M2 polarization of hepatic macrophages promotes extracellular matrix differentiation, HSC activation, and angiogenesis, becoming a key factor driving disease deterioration. Targeted inhibition of hepatic macrophage M2 polarization may represent an effective therapeutic strategy at this stage.

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3. Exercise-Mediated Macrophage Polarization in NAFLD Treatment

The efficacy of exercise in treating various obesity-related metabolic diseases, including NAFLD, has been widely validated and recognized, yet mechanistic investigations have not achieved breakthroughs. Given the close relationship between macrophage polarization and NAFLD pathogenesis, recent studies have begun exploring exercise effects on macrophage polarization and its potential role in NAFLD prevention and treatment [Figure 1: see original paper]. Systematic summarization of current research not only enhances understanding of macrophage polarization in NAFLD development but also holds significant importance for developing novel therapeutic strategies.

3.1 Effects of Exercise on Macrophage Polarization Research indicates that macrophages exhibit M1 phenotype characteristics when energy metabolism is glycolysis-dominant, whereas oxidative phosphorylation-dominant metabolism correlates with M2 phenotype [38,58]. Exercise directly modulates systemic energy metabolism; chronic aerobic exercise increases M2 macrophage phenotypic abundance [59-61], while acute high-intensity anaerobic exercise increases M1 macrophage phenotypic abundance [51,62-64]. Both human and animal studies demonstrate that moderate-intensity aerobic or resistance exercise activates peroxisome proliferator-activated receptor γ (PPARγ) signaling, reducing M1-related cytokines such as interferon-γ (IFN-γ), CCL2, TNF-α, and IL-6 while increasing M2-related markers including CD14, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), and IL-4, thereby regulating immune responses and preventing obesity-related metabolic diseases [60-61,65]. High-intensity exercise can also reverse obesity-induced M1 polarization by inhibiting nuclear factor B (NF- B) and Notch signaling pathways, increasing M2 abundance and suppressing pathogenic adipokine secretion to improve obesity-related metabolic diseases including hepatic steatosis [66-67]. In contrast to aerobic exercise, acute anaerobic exercise significantly elevates serum pro-inflammatory factors such as IL-6, TNF-α, and CCL2, increasing M1 polarization and inducing inflammatory responses [62,68]. However, this inflammatory response is transient and may relate to temporary increases in anaerobic metabolism-related enzymes such as creatine kinase (CK) [63] or tissue microstructural damage triggering stress-induced inflammation [64].

Therefore, various intensities of aerobic exercise can inhibit M1 polarization and promote M2 polarization, improving metabolic status and inflammatory responses, whereas anaerobic exercise produces transient opposite effects. The cumulative effects of long-term anaerobic training on macrophage polarization remain unreported.

3.2 Research Progress on Macrophage Polarization in Exercise-Based NAFLD Prevention Given exercise effects on macrophage polarization and the critical role of macrophage polarization in NAFLD progression, exploring

exercise-mediated macrophage polarization holds important clinical significance for NAFLD prevention and treatment across disease stages. Current exercise intervention studies primarily focus on early-stage NAFL and NASH, with limited research on advanced fibrosis with cirrhosis or hepatocellular carcinoma .

In early-stage NAFLD interventions, exercise has generated substantial research interest. High-intensity aerobic exercise demonstrates particularly pronounced effects on early NAFL, significantly improving cardiorespiratory fitness within short periods while promoting fat oxidation and ameliorating hepatic steatosis. Babu et al. [69] found that 12 weeks of high-intensity interval training in early-stage NAFLD patients reduced blood glucose and branched-chain amino acid concentrations in adipose tissue while activating the PPARγ/PGC-1α pathway to promote M2 polarization and alleviate hepatic steatosis. Studies by Cho et al. [70] and Linden et al. [71] similarly demonstrated that high-intensity exercise reduces M1 macrophage markers while increasing M2 markers, playing a key role in treating NAFL associated with obesity and impaired glucose tolerance. Increased IL-22 expression following high-intensity exercise is also considered an important factor promoting M2 polarization, associated with alleviating hepatic inflammation and preventing NAFL progression to NASH [58,72-73].

When disease progresses to NASH, most patients develop overt symptoms, leading researchers to employ moderate-intensity aerobic exercise interventions for safety considerations. Fredrickson et al. [74] used flow cytometry to demonstrate that moderate-intensity aerobic exercise reduces pro-inflammatory factors including IFN-γ, TNF-α, CCL2, and IL-6 in NASH mouse hepatocytes while significantly increasing anti-inflammatory IL-10 expression. As previously discussed, exercise can modulate macrophage polarization by affecting metabolic characteristics [51,59-61]. Luo et al. [75] simulated aerobic exercise through intermittent hypoxia stimulation in mice, finding that hypoxia upregulated genes related to aerobic metabolism including adrenergic receptor $ 3(ADR 3), carnitine palmitoyltransferase 1A (CPT1A), adipose triglyceride lipase (ATGL), and PGC-1 , thereby increasing M2 macrophage markers arginase 1 (Arg1) and CD206 expression and ameliorating high-fat diet-induced NASH. Dini zetal.[76] also found that moderate-intensity aerobic exercise improved insulin re
PPAR $ signaling. A systematic review indicated that moderate-intensity aerobic exercise activates M2 macrophage phenotypic abundance, demonstrating significant efficacy in treating NASH through mechanisms related to AMPK, uncoupling protein 1 (UCP-1), and PPARγ expression and adiponectin secretion [77]. Recent studies further confirm that aerobic exercise promotes M2 polarization and alleviates insulin resistance by activating AMPK and inhibiting c-Jun N-terminal kinase (JNK) signaling, thereby reducing inflammation, oxidative stress, and ameliorating NASH [78-80].

Although exercise interventions have been conducted in cirrhotic and hepatocellular carcinoma patients, these studies primarily focus on psychological and quality-of-life improvements without exploring relationships with hepatic macrophages [81-82].

In summary, exercise is an effective intervention for NAFLD. In early-

stage NAFLD, various intensities of aerobic exercise can inhibit exogenous macrophage infiltration or Kupffer cell M1 polarization, thereby suppressing M1/M2 ratio elevation and demonstrating significant preventive and therapeutic effects. Exercise also exerts positive effects in advanced NAFLD stages, though direct links to macrophage polarization remain undiscovered. Current research suggests that hepatic macrophage polarization exhibits distinct pathological features across NAFLD stages. In early hepatic steatosis and steatohepatitis, the M1/M2 ratio increases dramatically, causing hepatic inflammatory damage. Both exercise and pharmacological interventions can prevent and treat disease by reducing the M1/M2 ratio. In fibrosis-cirrhosis and hepatocellular carcinoma stages, stress-induced M2 polarization occurs, and strategies inhibiting M2 polarization may benefit disease prognosis, though no targeted pharmacological interventions against M2 polarization in advanced NAFLD have been reported.

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4. Summary and Outlook

Macrophages exhibit marked tissue heterogeneity and plasticity, making methodological approaches decisive in this research field. Some studies have employed advanced techniques including single-cell genomics and transcriptomics sequencing, genetically encoded fluorescent labeling, and high-throughput phenotypic screening to localize macrophage origins, enabling identification of phenotypic and distributional characteristics of resident Kupffer cells versus infiltrating macrophages across NAFLD stages. Although some studies have assessed macrophage polarization status solely based on surface marker expression, neglecting macrophage origin, they nonetheless provide valuable foundational research. While exercise efficacy in NAFLD prevention and treatment has been extensively confirmed, mechanistic investigations have largely remained at the metabolic level. Recent research has begun focusing on the macrophage-exercise-NAFLD relationship. Analysis of limited current studies reveals that moderate-intensity aerobic exercise effectively controls NAFLD at all stages except hepatocellular carcinoma, while high-intensity aerobic exercise also demonstrates significant effects on early hepatic steatosis. These effects are associated with aerobic exercise-mediated inhibition of macrophage infiltration or Kupffer cell M1 polarization, thereby reducing the M1/M2 ratio. Although exercise interventions exist for fibrosis-cirrhosis and hepatocellular carcinoma, their relationships with hepatic macrophages remain unexplored.

Current research limitations include that some studies measure macrophage polarization status solely through surface marker expression levels. Macrophage polarization is a dynamic process accompanied by efferocytosis, necessitating more precise detection and tracking technologies to explore activity characteristics of hepatic macrophages from different origins in NAFLD pathogenesis. Such advances would be clinically significant for developing novel targeted therapies.

Figure 1. Relationship between macrophage polarization and pathological processes of non-alcoholic fatty liver disease and the therapeutic effects of exercise

Note: In healthy liver, resident Kupffer macrophages maintain dynamic equilibrium between pro-inflammatory M1 and anti-inflammatory M2 phenotypes. Under obese conditions, hepatic steatosis induces bone marrow-derived monocyte infiltration, increasing the M1/M2 ratio and secreting pro-inflammatory factors that gradually induce non-alcoholic steatohepatitis. At this stage, persistent macrophage infiltration is accompanied by markedly increased M1 polarization of Kupffer cells, which secrete abundant pro-inflammatory factors and activate hepatic stellate cells, promoting hepatic inflammation deterioration and gradual progression to fibrosis. During fibrosis-cirrhosis and hepatocellular carcinoma stages, hepatic macrophages undergo stress-induced M2 polarization, exacerbating disease deterioration through mechanisms including promoting extracellular matrix differentiation and hepatic stellate cell activation. Early-stage exercise of varying intensities can inhibit macrophage infiltration and Kupffer cell M1 polarization, thereby reducing the M1/M2 ratio and delaying disease progression. In advanced disease stages, exercise also exerts positive effects, though direct links to macrophage polarization remain undiscovered. AMPK=adenosine monophosphate-activated protein kinase, CCL2=C-C motif chemokine ligand 2, CX3CL1=C-X3-C motif chemokine ligand 1, CD44=transmembrane glycoprotein CD44, HSC=hepatic stellate cell, IL=interleukin, KC=Kupffer cell, NLRP3=nucleotide-binding oligomerization domain, leucine-rich repeat-containing protein 3, p38α=p38 mitogen-activated protein kinase, PGC-1α=peroxisome proliferator-activated receptor γ coactivator α, PPARγ=peroxisome proliferator-activated receptor γ, PGE2=prostaglandin E2, TLR4=Toll-like receptor 4, TNF-α=tumor necrosis factor α, UCP-1=uncoupling protein 1.

Table 1. Summary of studies on exercise-mediated macrophage polarization in the treatment of non-alcoholic fatty liver disease progression

Study	Year	Model	Exercise Protocol	Disease Stage	Polarization/Mechanism	Key Findings
Babu [69]	2022	NAFLD patients	High-intensity interval exercise (85% VO_2max for 4 min intervals with 2-4 min rest)	NAFL	M1↓ M2↑ SM↓ PPARγ↑ PGC-1α↑	Regulates lipid metabolism, improves NAFLD
Shanaki [66]	2020	Wistar rats	High-intensity interval exercise ($5\$\times 2 mins prints at 80-90\{2\} max with 1 min intervals) \| NAFL \| M1 \downarrow M2 \uparrow IL-10 \uparrow CD163 \uparrow CD206 \uparrow TNF- \downarrow IL-6 \downarrow NF-\kappa B \downarrow \| Reduces inflammation, improves obesity-induced hepatic steatosis \| \| Cho [70] \| 2015 \| C57BL/6 mice \| High-intensity interval exercise (12 \times 1 min intervals at 17 m/min) \| NAFL \| M1 \downarrow M2 \uparrow AMPK \uparrow \| Delays hepatic steatosis associated with obesity and glucose intolerance \| \| Linden [71] \| 2015 \| C intensity interval exercise (6 \times 2.5 min/dat 40 m/min, 15 \uparrow AMPK \uparrow \| Enhances fat phagocytosis, regulates NASH \| \| Luo [75] \| 2022 \| C57BL/6 mice \| Chronic inte$ for 1 h daily)	NAFL	M1↓ M2↑ CD11c↓ TNF-α↓ IL-1β↓ CD206↑	Alters hepatic macrophage polarization, prevents disease progression

Study	Year	Model	Exercise Protocol	Disease Stage	Polarization/Mechanism	Key Findings
Li [79]	2021	C57BL/6J mice	Aerobic swimming training (60 min daily forced swimming)	NASH	M2↑ AMPK↑ SIRT1↑ LC3↑ JNK↓	Promotes M2 macrophage phenotype, inhibits M1 macrophages, reduces infiltration, ameliorates NASH
Fredrickson [74]	2021	C57BL/6J mice	Moderate-intensity exercise (starting at 13 m/min, increasing 1 m/min every 1-2 weeks to 20 m/min)	NASH	M1↓ M2↑ MCP-1↓ TNF-α↓ INF-γ↓ IL-6↓ IL-10↑	Reduces lipid peroxidation, delays NASH progression
Souza [67]	2018	Obese men	Moderate-intensity continuous exercise (70% HRmax for 20 min)	NASH	M2↑ IL-4↑ IFN-γ↓ IL-6↓	Enhances lipophagy, improves NASH

Note: ADR3=adrenergic receptor $ 3, ATGL = adiposetriglyceridelipase, AMPK = adenosinemonophosphate−activatedproteinkinase, CPT1A = carnitinepalmitoyltransferase1A, CD163and interleukin, IFN− $=interferon γ, JNK=c-Jun N-terminal kinase, LC3=microtubule-associated protein light chain 3, MCP1=monocyte chemoattractant protein 1, OLETF rats are spontaneous type 2 diabetes model animals derived from Long-Evans rats, PPARs=peroxisome proliferator-activated receptors, PGC-1α=peroxisome proliferator-activated receptor γ coactivator 1α, SIRT1=sirtuin 1, SM=sphingomyelin, TNF-α=tumor necrosis factor α, UCP-1=uncoupling protein 1.

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