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Effects of High-Intensity Interval Training and Moderate-Intensity Continuous Training on PGC-1α, SIRT3, and Non-Alcoholic Fatty Liver Disease: A Narrative Review

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Abstract

Background & Objectives: This narrative review examines the effects of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) on key mitochondrial biomarkers, namely peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and sirtuin 3 (SIRT3), and evaluates their therapeutic roles in metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD).

Materials & Methods: A systematic literature search was conducted in the Scopus, PubMed, ScienceDirect, and Elsevier databases using the keywords "HIIT," "MICT," "PGC-1α," "SIRT3," and "MASLD," with no temporal restrictions applied. Studies published up to October 2025 were included. The initial search yielded approximately 600 articles; following duplicate removal and title and abstract screening, 83 relevant studies were selected for inclusion. Priority was given to recent evidence published between 2022 and 2025 that incorporated the updated MASLD nomenclature.

Results: Both HIIT and MICT significantly upregulate PGC-1α and SIRT3 expression, thereby enhancing mitochondrial biogenesis, reducing oxidative stress, and improving hepatic lipid metabolism. These molecular adaptations are associated with clinically meaningful outcomes, including reduced hepatic fat accumulation, improved insulin sensitivity, and enhanced liver function. HIIT tends to elicit more rapid molecular and metabolic adaptations, whereas MICT is more consistently associated with sustained long-term benefits.

Conclusion: HIIT and MICT represent effective, evidence-based exercise interventions for the management of MASLD through modulation of mitochondrial signaling pathways. HIIT may be preferable when time efficiency is a priority, whereas MICT may be more suitable for long-term adherence. An individualized exercise prescription, beginning with MICT and progressively incorporating HIIT, is recommended. The primary limitations of this review include its narrative design and the potential for publication bias; therefore, future large-scale randomized controlled trials across diverse populations are warranted.

Keywords: PGC-1α, SIRT3, HIIT, MICT, MASLD

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as non-alcoholic fatty liver disease (NAFLD),

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is characterized by excessive triglyceride accumulation in hepatocytes in the absence of significant alcohol consumption, hepatotoxic drug exposure, or other chronic liver diseases (1). This review adheres to the updated MASLD nomenclature, which has replaced NAFLD in contemporary scientific literature, reflecting an international consensus emphasizing the central role of metabolic dysfunction in disease pathogenesis (64). Consequently, the term MASLD is consistently used throughout this review to ensure alignment with current diagnostic and research standards.

MASLD encompasses a disease spectrum ranging from simple steatosis, defined by hepatic fat content exceeding 5% of liver weight, to metabolic dysfunction-associated steatohepatitis (MASH), formerly termed non-alcoholic steatohepatitis (NASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma (2–4). With a global prevalence of approximately 25%, MASLD is strongly associated with the increasing incidence of obesity, type 2 diabetes mellitus, insulin resistance, dyslipidemia, and metabolic syndrome (5). Despite substantial advances in elucidating its pathophysiology, no disease-specific pharmacological therapy has yet been approved, rendering lifestyle modification, particularly dietary management and structured physical activity, the cornerstone of MASLD treatment (1). Exercise exerts protective effects against MASLD through multiple mechanisms, including weight reduction, enhancement of insulin sensitivity, attenuation of oxidative stress, modulation of inflammatory pathways, and improvement of lipid metabolism (6).

Among exercise modalities, HIIT, characterized by brief bouts of vigorous exercise performed at 85–95% of maximal heart rate interspersed with recovery periods, and MICT, involving sustained activity at 60–75% of maximal heart rate, have received considerable scientific attention (7).

At the molecular level, exercise influences key regulatory proteins, most notably PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), a master regulator of mitochondrial biogenesis, and SIRT3 (sirtuin 3), a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase localized predominantly within mitochondria (8). Accordingly, this narrative review synthesizes current evidence regarding the effects of HIIT and MICT on mitochondrial regulators, specifically PGC-1α and SIRT3, and their implications for clinical and metabolic outcomes in MASLD.

Pathophysiology of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Molecular Mechanisms of MASLD Progression

The pathogenesis of MASLD is complex and multifactorial. The classical "two-hit" hypothesis was initially proposed to explain disease progression toward MASH. The first hit involves hepatic lipid accumulation, primarily driven by insulin resistance and elevated circulating free fatty acids. The second hit encompasses oxidative stress, lipid peroxidation, mitochondrial dysfunction, and inflammatory responses, ultimately resulting in hepatocellular injury and disease progression (9).

More recently, the "multiple-hit" model has supplanted this framework, incorporating the combined contributions of impaired lipid metabolism, insulin resistance, gut microbiota dysbiosis, mitochondrial dysfunction, oxidative stress, defective autophagy, and genetic susceptibility to MASLD progression (10).

Role of mitochondrial dysfunction in MASLD

Mitochondria play a central role in hepatic lipid oxidation and cellular energy production. Mitochondrial dysfunction represents a key pathogenic mechanism in MASLD. In affected individuals, reductions in mitochondrial biogenesis and fatty acid oxidation capacity are observed, accompanied by increased production of reactive oxygen species and diminished efficiency of the electron transport chain (11).

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The importance of PGC-1α and SIRT3 in mitochondrial function and liver metabolism

PGC-1α is a master regulator of mitochondrial biogenesis and cellular energy metabolism. It interacts with multiple transcription factors, including peroxisome proliferator-activated receptor gamma (PPARγ), nuclear respiratory factor 1 (NRF1), and nuclear respiratory factor 2 (NRF2), thereby regulating genes involved in mitochondrial biogenesis, oxidative phosphorylation, and lipid metabolism (12).

SIRT3 is an NAD^+-dependent mitochondrial deacetylase that plays a critical role in regulating energy metabolism, antioxidant defense, and mitochondrial homeostasis. Through deacetylation, SIRT3 modulates the activity of key mitochondrial enzymes, including superoxide dismutase 2, acetyl-CoA synthetase 2, and long-chain acyl-CoA dehydrogenase (13).

In individuals with MASLD, both the expression and activity of PGC-1α and SIRT3 are markedly reduced, contributing to impaired mitochondrial function, decreased fatty acid oxidation, and heightened oxidative stress. Consequently, therapeutic strategies aimed at enhancing PGC-1α and SIRT3 activity may be of substantial clinical relevance in MASLD management (14). Notably, PGC-1α directly stimulates SIRT3 gene expression, forming a regulatory feedback loop that promotes mitochondrial efficiency (15, 16). This interaction has emerged as a promising therapeutic target, with SIRT3 activators, such as honokiol, demonstrating potential benefits in reducing hepatic steatosis and fibrosis (17).

Role of the Gut Microbiome in MASLD and Exercise-Induced Modulation

The gut microbiome plays a pivotal role in MASLD pathogenesis through the gut–liver axis. Dysbiosis, characterized by reduced microbial diversity and increased abundance of pathogenic taxa, promotes endotoxemia, systemic inflammation, and insulin resistance, thereby exacerbating hepatic steatosis (18). Both HIIT and MICT modulate gut microbial composition by increasing beneficial bacterial populations, such as *Akkermansia* and *Bifidobacterium*, and enhancing short-chain fatty acid production. These adaptations improve intestinal barrier integrity and reduce lipopolysaccharide translocation to the liver (19–22).

Recent studies published between 2022 and 2025 suggest that HIIT may be more effective than MICT in restoring gut microbiome diversity in experimental MASLD models, leading to reduced hepatic lipid accumulation through coordinated effects on mitochondrial remodeling and adipokine signaling (23, 24). These exercise-induced microbiome adaptations appear to act synergistically with dietary interventions, thereby amplifying therapeutic efficacy (19, 21, 22).

Exercise and MASLD

The role of physical activity in the prevention and treatment of MASLD

Regular physical activity plays a central role in both the prevention and treatment of MASLD. According to current clinical guidelines, a minimum of 150 minutes of moderate-intensity aerobic exercise per week is recommended for patients with MASLD (25). Physical activity improves MASLD through multiple interrelated mechanisms, including reductions in body weight, improvements in insulin sensitivity, decreases in hepatic fat accumulation, enhancement of mitochondrial function, attenuation of oxidative stress, and modulation of inflammatory pathways (26).

Dose–response analyses demonstrate that higher-intensity exercise modalities, such as HIIT performed at 85–95% of maximum heart rate for 3–5 sessions per week (20–40 minutes per session), reduce hepatic fat content more effectively than lower exercise volumes in individuals with MASLD. However, these benefits appear to plateau beyond approximately 250 minutes of exercise per week (6, 27).

Long-term exercise interventions lasting longer than six months are associated with

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sustained improvements in insulin sensitivity and hepatic enzyme profiles in patients with MASLD, although adherence rates tend to decline over time (6, 28). Exercise responsiveness varies across populations; older adults (over 60 years of age) and female patients demonstrate higher adherence to MICT, whereas individuals with severe MASLD derive greater benefit from supervised HIIT protocols (28, 29).

Detailed exercise prescriptions commonly include HIIT protocols consisting of four 4-minute intervals at 90% of maximal heart rate with 3-minute recovery periods, performed three times per week, and MICT protocols involving 45–60 minutes of continuous exercise at 60–70% of maximal heart rate, performed four to five times per week (6).

To maximize reductions in hepatic fat content, exercise interventions should be combined with dietary strategies, particularly adherence to a Mediterranean-style diet rich in fruits, nuts, seeds, whole grains, fish, and poultry (30). In advanced cases of MASLD, where approved pharmacological therapies remain unavailable, maintaining a healthy lifestyle and avoiding ultra-processed foods, red and processed meats, sugar-sweetened beverages, and tobacco use is essential (30).

Implementation strategies, including telehealth-based monitoring, motivational interviewing, and structured group exercise programs, have been shown to enhance long-term adherence to lifestyle interventions in patients with MASLD (28).

High-intensity interval training (HIIT)

HIIT consists of short bouts of vigorous exercise, typically lasting between 30 seconds and 4 minutes, performed at 85–95% of maximal heart rate or maximal oxygen uptake, interspersed with periods of rest or low-intensity recovery. Numerous studies have demonstrated that HIIT can elicit physiological adaptations comparable to, or greater than, those induced by MICT while requiring substantially less total exercise time (31–33).

Recent investigations published between 2022 and 2025 indicate that HIIT and MICT are similarly effective in reducing hepatic fat content in patients with MASLD, although HIIT requires significantly less time per training session. Reported long-term adherence rates are approximately 63% for unsupervised HIIT programs and 92% for supervised MICT protocols (6, 34).

Moderate Intensity Continuous Training (MICT)

MICT involves sustained aerobic exercise lasting 30–60 minutes at an intensity corresponding to 60–75% of maximal heart rate or maximal oxygen uptake. This modality has long been regarded as a foundational approach for improving cardiorespiratory fitness and metabolic health (35).

In the context of MASLD, MICT supports long-term disease management, particularly among older adults and individuals with advanced disease stages, such as metabolic dysfunction-associated steatohepatitis or hepatic fibrosis. Compared with HIIT, MICT is associated with higher long-term adherence rates, averaging 92.5% ± 10.6% in supervised settings, and a lower incidence of adverse cardiovascular or musculoskeletal events (25, 34, 36). Accumulating evidence indicates that a minimum of 150 minutes per week of MICT improves hepatic steatosis and liver inflammation, both in the presence and absence of modest weight loss (25).

The Effect of HIIT and MICT on PGC-1α

Mechanism of regulation of PGC-1α expression by exercise

Exercise modulates PGC-1α expression and activity through several well-characterized intracellular signaling pathways:

1. **AMP-activated protein kinase (AMPK) pathway:** Muscle contraction increases the AMP-to-ATP ratio, leading to activation of AMPK, which directly phosphorylates and activates PGC-1α (37, 38).

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2. **Calcium/calmodulin-dependent protein kinase (CaMK) pathway:** Exercise-induced elevations in intracellular calcium activate CaMK, thereby enhancing transcriptional upregulation of PGC-1α (39).

3. **SIRT1 pathway:** Sirtuin 1, an NAD^+-dependent deacetylase encoded by the *SIRT1* gene, is activated by exercise-induced increases in the NAD^+/NADH ratio. Activated SIRT1 deacetylates and functionally activates PGC-1α, promoting mitochondrial biogenesis (24, 40) (Figure 1A, B).

Comparison of the effects of HIIT and MICT on PGC-1α expression and activity

Evidence indicates that both HIIT and MICT significantly increase PGC-1α expression and activity, although the magnitude and temporal pattern of adaptation differ between modalities. Owing to its higher intensity, HIIT typically induces a more rapid and pronounced upregulation of PGC-1α (42).

Little et al. demonstrated that only two weeks of HIIT training, comprising ten sessions, resulted in a significant increase in PGC-1α protein content in human skeletal muscle (43). Similarly, Bartlett et al. reported that a single session of HIIT elicited a greater increase in PGC-1α gene expression compared with energy-matched MICT (44).

Conversely, long-term MICT has also been shown to substantially increase PGC-1α expression. Russell et al. observed that six weeks of moderate-intensity endurance training increased skeletal muscle PGC-1α protein content by approximately 66% (45).

In MASLD-specific contexts, animal studies indicate that both exercise modalities enhance hepatic PGC-1α expression. Oh et al. reported that eight weeks of HIIT in MASLD mouse models increased hepatic PGC-1α expression, improved mitochondrial function, and reduced hepatic steatosis (46).

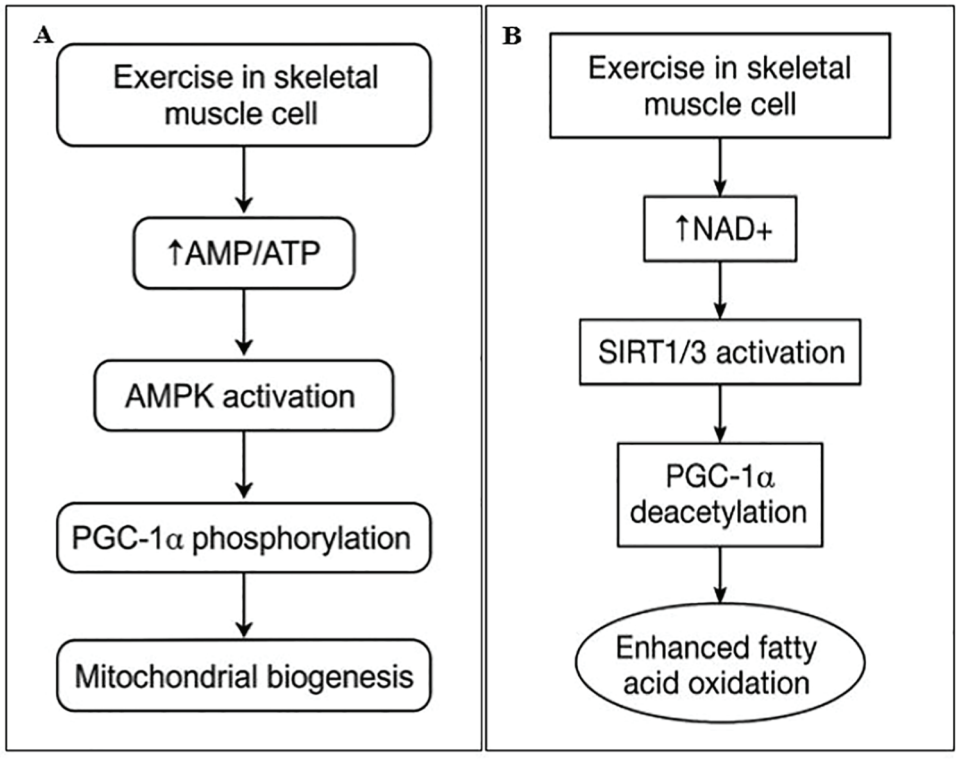

Figure 1. (A, B). Detailed diagram of PGC-1α signaling pathway in exercise and mitochondrial biogenesis (41). AMP: adenosine monophosphate, ATP: adenosine triphosphate, NAD+: nicotinamide adenine diphosphate

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Similarly, Linden et al. demonstrated that sixteen weeks of MICT increased hepatic PGC-1α expression, improved lipid metabolism, and attenuated histopathological features of MASLD (47).

Recent meta-analyses published between 2022 and 2025 further indicate that HIIT significantly reduces intrahepatic lipid content (P = 0.01; SMD = −0.56; 95% CI = −0.99 to −0.13) and liver enzyme concentrations, including alanine aminotransferase (ALT) (P = 0.0006; SMD = −0.61; 95% CI = −0.95 to −0.26) and aspartate aminotransferase (AST) (P = 0.03; SMD = −0.43; 95% CI = −0.81 to −0.05), in patients with severe MASLD. These improvements are likely mediated, at least in part, by enhanced mitochondrial biogenesis, for which PGC-1α serves as a key molecular marker (48).

Effect of HIIT and MICT on SIRT3

Mechanism of regulation of SIRT3 expression by exercise

Sirtuin 3 (SIRT3) is a mitochondrial deacetylase that plays a critical role in the regulation of energy metabolism and antioxidant defense. Exercise modulates SIRT3 expression and activity through several interrelated mechanisms:

1. **Increased NAD^+/NADH ratio:** Exercise elevates the mitochondrial NAD^+/NADH ratio, thereby promoting SIRT3 activation (49).

2. **Upregulation of PGC-1α expression:** PGC-1α functions as a positive transcriptional regulator of SIRT3; therefore, exercise-induced increases in PGC-1α expression lead to enhanced SIRT3 transcription (16).

3. **Reduction of oxidative stress:** Regular physical activity attenuates oxidative stress, which indirectly promotes increased SIRT3 expression and activity (50).

The PGC-1α–SIRT3 signaling loop activated by exercise (HIIT or MICT) involves an increase in the NAD^+/NADH ratio, activation of SIRT3, subsequent upregulation of PGC-1α expression, and enhanced SIRT3 transcription. This cascade promotes deacetylation of mitochondrial enzymes, including superoxide dismutase 2 and long-chain acyl-CoA dehydrogenase, resulting in reduced reactive oxygen species production and increased fatty acid oxidation. SIRT3 agonists have therefore been proposed as potential pharmacological targets capable of mimicking exercise-induced adaptations (Figure 2).

Comparison of the effects of HIIT and MICT on SIRT3 expression and activity

Available evidence indicates that both HIIT and MICT significantly increase SIRT3 expression and enzymatic activity. Vargas-Ortiz et al. demonstrated that 12 weeks of HIIT training in mice significantly upregulated SIRT3 expression in skeletal muscle (54).

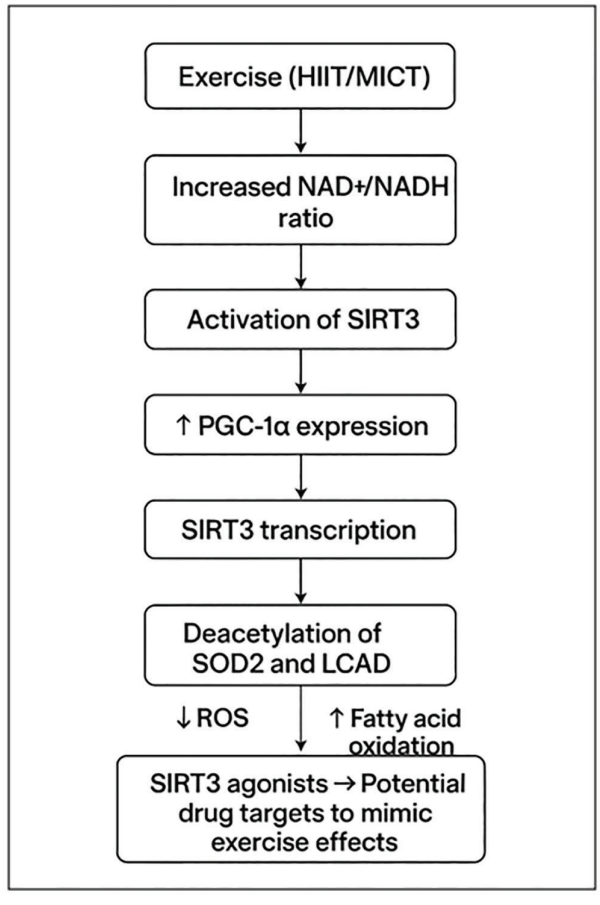

Figure 2. Signaling pathways involve PGC-1α/SIRT3 loop (16, 48-53). SOD: superoxide dismutase, LCAD: low-chin acyl coa deydrogenase, ROS: reactive oxygen species

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Similarly, Gurd et al. reported that chronic muscle contraction increased mitochondrial SIRT3 protein expression in mouse skeletal muscle through an AMPK-independent mechanism (55).

With respect to MICT, Lanza et al. observed that individuals engaged in long-term endurance training exhibited higher skeletal muscle SIRT3 levels compared with sedentary controls (56). In addition, Brandauer et al. reported that eight weeks of moderate-intensity endurance training increased both SIRT3 expression and activity in mouse skeletal muscle (57).

In the context of MASLD, direct evidence regarding hepatic SIRT3 modulation by HIIT and MICT remains limited. However, Cho et al. demonstrated that eight weeks of aerobic treadmill exercise in C57BL/6 mice fed a high-fat diet reduced hepatic steatosis, improved glucose tolerance, and decreased insulin resistance, effects that were associated with increased hepatic expression of peroxisome proliferator-activated receptor alpha and SIRT1 (58). Furthermore, Heinle et al. reported that exercise training, including HIIT, improves fatty acid metabolism and reduces hepatic inflammation in patients with MASLD, likely through activation of the AMPK and PPARα/γ signaling pathways (26).

Effect of HIIT and MICT on MASLD Parameters

Effect on Biochemical Parameters

Both HIIT and MICT favorably modulate biochemical markers associated with MASLD:

1. **Liver enzymes:** Evidence indicates that both exercise modalities reduce serum alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase levels. In a meta-analysis, Winn et al. demonstrated that HIIT significantly improved hepatic steatosis and liver enzyme concentrations, supporting its utility as a time-efficient intervention for MASLD management (59). Similarly, Hong et al. reported that exercise training significantly reduced ALT and AST levels in patients with MASLD, particularly among individuals aged 30 to 49 years (60).

2. **Lipid profile:** Both HIIT and MICT improve lipid profiles in patients with MASLD (61). Guo et al. demonstrated that 12 weeks of HIIT and traditional aerobic training improved physical fitness and biochemical indices in MASLD patients, with HIIT conferring greater benefits in cardiorespiratory fitness, muscular strength, and metabolic, inflammatory, and oxidative stress markers, underscoring its potential as a time-efficient therapeutic strategy (62).

3. **Insulin resistance:** Both exercise modalities significantly enhance insulin sensitivity. Cassidy et al. reported that 12 weeks of HIIT resulted in a 39% reduction in the homeostatic model assessment of insulin resistance (HOMA-IR) in patients with MASLD (63). Likewise, Hashida et al. demonstrated that 12 weeks of MICT reduced HOMA-IR by approximately 27% in this population (64).

Long-term interventions exceeding 12 months show sustained metabolic benefits when exercise is combined with dietary modification; however, adherence-enhancing strategies, including app-based monitoring, are essential for maintaining these effects (65).

Effects on Liver Fat Content

Reduction of hepatic fat content represents a primary therapeutic goal in MASLD, and both HIIT and MICT have demonstrated efficacy in this regard. Hallsworth et al. reported that 12 weeks of HIIT resulted in a 39% reduction in liver fat content, as measured by magnetic resonance imaging, independent of weight loss (66). Similarly, Johnson et al. observed a 21% reduction in liver fat content measured by magnetic resonance spectroscopy following four weeks of MICT (67).

Comparative analyses suggest that HIIT may confer superior reductions in hepatic fat content. Winn et al. demonstrated that 12 weeks of HIIT produced a 39% reduction in liver fat compared with a 25% reduction achieved with MICT (60).

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Consistent with these findings, a meta-analysis by Smart et al. confirmed that HIIT yielded a greater reduction in liver fat content than MICT, as indicated by standardized mean differences of −0.92 for HIIT and −0.57 for MICT (68).

Effect on Liver Enzymes

aEffect on Insulin Sensitivity

Improved insulin sensitivity represents a key mechanistic pathway underlying exercise-induced improvement in MASLD. Jelleyman et al. demonstrated that HIIT produced greater improvements in insulin sensitivity than MICT, with standardized mean differences of 0.49 and 0.20, respectively (70). Dose–response analyses suggest that three to four exercise sessions per week may be optimal for elderly patients (27) (Tables 1 and 2).

Molecular mechanisms of the effects of HIIT and MICT on fatty liver

Increased mitochondrial biogenesis

Exercise-induced upregulation of PGC-1α accelerates mitochondrial biogenesis, enhances oxidative capacity, and reduces hepatic lipid accumulation (51). HIIT exerts a more pronounced stimulatory effect on mitochondrial biogenesis, primarily due to its greater capacity to increase PGC-1α expression compared with MICT (31).

Improved mitochondrial function

Exercise-mediated increases in SIRT3 expression promote the deacetylation and activation of key mitochondrial enzymes, thereby improving overall mitochondrial function (71). Enhanced mitochondrial efficiency leads to increased fatty acid oxidation and reduced hepatic lipid accumulation (72, 73). The interaction between PGC-1α and SIRT3 amplifies these effects through activation of the AMPK signaling pathway, highlighting PGC-1α agonists as potential therapeutic targets (74).

Increased Fatty Acid Oxidation

Exercise enhances fatty acid oxidation by upregulating enzymes involved in mitochondrial beta-oxidation, including carnitine palmitoyltransferase 1 and medium-chain acyl-CoA dehydrogenase (75, 76). HIIT produces a stronger stimulatory effect on fatty acid oxidation, attributable to more robust AMPK activation and a greater increase in PGC-1α expression compared with MICT (31, 43).

Table 1. Comparison of HIIT vs. MICT Effects on MASLD Parameters.

Parameter	HIIT	MICT
PGC-1α Expression	Upregulates expression, enhancing mitochondrial biogenesis	Upregulates expression, supporting mitochondrial function
SIRT3 Expression	Increases expression, reducing oxidative stress	Increases expression, aiding mitochondrial protection
Liver Enzymes (ALT, AST)	Reduces ALT by 24.8% and AST by 19.5% in 12 weeks, improving liver function	Reduces ALT by 14.5% and AST by 11.8% in 12 weeks, improving liver function
Insulin Sensitivity	Improves HOMA-IR (SMD: 0.49) in 12 weeks, potentially faster	Improves HOMA-IR (SMD: 0.20) in 12 weeks, suitable for long-term management
Liver Fat Content	Reduces liver fat by 39% in 12 weeks, independent of weight loss; 39% vs. 25% reduction compared to MICT; SMD: -0.92	Reduces liver fat by 21% in 4 weeks; 25% in 12 weeks; SMD: -0.57

Table 2. Dose-Response and Population-Specific Recommendations.

Parameter	Intensity/Frequency/Duration	Population Considerations
Liver Fat Reduction	HIIT: 85-95% HRmax, 3-5x/week, 20-40 min	More effective in males, moderate severity
Insulin Sensitivity	MICT: 60-75% HRmax, 5x/week, 45-60 min	Better adherence in females, elderly
Long-Term Adherence	Combined with diet/pharmacotherapy	Telehealth for barriers

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Reduces oxidative stress

Exercise-induced upregulation of SIRT3 leads to deacetylation and activation of superoxide dismutase 2, a critical mitochondrial antioxidant enzyme (77). This enhancement of mitochondrial antioxidant defenses reduces oxidative stress and protects hepatocytes from oxidative damage.

Improved insulin sensitivity

Exercise training improves insulin sensitivity by increasing glucose transporter type 4 expression and enhancing insulin signaling pathways (78). Numerous animal and human studies have demonstrated that impaired GLUT4-mediated glucose uptake represents a primary mechanism underlying insulin resistance (79). Evidence suggests that higher-intensity exercise induces greater increases in GLUT4 expression when exercise duration is matched (80). However, other studies have reported that when caloric expenditure and workload are equivalent, exercise performed at intensities of 40% and 80% of peak oxygen consumption results in comparable increases in GLUT4 mRNA and protein expression in human skeletal muscle (81).

The increase in skeletal muscle glucose transport during exercise is primarily mediated by translocation of GLUT4 from intracellular compartments to the sarcolemma and T-tubules, although changes in intrinsic transporter activity may also contribute (82). Improved insulin sensitivity reduces hepatic de novo lipogenesis and contributes to decreased fat accumulation in the liver (83). Exercise-induced modulation of the gut microbiome further enhances these metabolic benefits (23).

Discussion

This narrative review synthesizes current evidence demonstrating that both HIIT and MICT are effective exercise-based interventions for the management of MASLD. These modalities promote mitochondrial biogenesis and function through upregulation of PGC-1α and SIRT3, resulting in significant reductions in hepatic fat content, liver enzyme concentrations, and oxidative stress, alongside improvements in insulin sensitivity and inflammatory status (6, 48).

Comparative analyses indicate that HIIT may confer superior benefits within shorter time frames, particularly with respect to increasing PGC-1α and SIRT3 expression and reducing intrahepatic lipid content (standardized mean difference: −0.92 for HIIT vs. −0.57 for MICT). These effects are likely mediated by greater metabolic stress and stronger activation of AMPK and p38 mitogen-activated protein kinase signaling pathways (42, 68).

Nevertheless, MICT remains a highly valuable exercise modality, especially for older adults and individuals with advanced MASLD, owing to higher long-term adherence rates, averaging 92.5% ± 10.6% in supervised settings, and a lower risk of cardiovascular or musculoskeletal complications (25, 34).

Limitations, Future Directions, and Clinical Implications

This review has several limitations, including its reliance on narrative synthesis, heterogeneity among included study designs, and a limited number of long-term studies exceeding one year, particularly in diverse populations. Future research should prioritize large-scale randomized controlled trials examining exercise-induced gut microbiome alterations, given their role in MASLD progression via the gut–liver axis (19, 23, 24), as well as sex-specific responses and the integration of structured exercise with emerging pharmacological therapies.

From a clinical standpoint, assessment of MASLD severity should precede exercise prescription, with initial implementation of MICT in high-risk patients to enhance safety and long-term adherence (28). Combining exercise interventions with adherence to a Mediterranean-style diet may further optimize therapeutic outcomes (30). Additionally, digital health strategies, including app-based tracking

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and telehealth monitoring, represent promising tools for improving sustained adherence (28).

Conclusion

Both HIIT and MICT significantly improve clinical and molecular parameters of MASLD by enhancing the expression and activity of PGC-1α and SIRT3. These adaptations lead to reductions in hepatic fat content and liver enzyme levels, alongside improvements in insulin sensitivity and attenuation of oxidative stress and inflammation.

Comparative evidence suggests that HIIT is generally more effective than MICT, particularly in upregulating mitochondrial regulators and reducing hepatic lipid accumulation. This enhanced efficacy is likely attributable to stronger activation of AMPK and p38 MAPK signaling pathways, greater increases in the NAD^+/NADH ratio, and heightened metabolic stress. Given the time constraints faced by many individuals, HIIT represents a time-efficient exercise strategy capable of producing equal or superior benefits relative to MICT.

Nevertheless, both HIIT and MICT remain valid and effective therapeutic options for MASLD management. The optimal exercise modality should be individualized based on patient tolerance, comorbidities, adherence capacity, personal preferences, and availability of clinical supervision.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization: Fatemeh Heiat and Manzar Banoo Shojaei Fard; Methodology: Fatemeh Heiat; Literature search and data curation: Fatemeh Heiat; Formal analysis and interpretation: Fatemeh Heiat and Manzar Banoo Shojaei Fard; Writing—original draft preparation: Fatemeh Heiat; Writing—review and editing: Manzar Banoo Shojaei Fard; Visualization: Fatemeh Heiat; Supervision: Manzar Banoo Shojaei Fard. All authors have read and agreed to the published version of the manuscript.

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