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Exercise as Medicine: The Impact of Exercise Training on Nonalcoholic Fatty Liver Disease

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Abstract

Purpose of review: Nonalcoholic fatty liver disease (NAFLD) is a leading cause of global liver disease. Because current pharmacologic treatments are ineffective, lifestyle change centered on exercise remains the most effective NAFLD treatment. The aim of this systematic review is to summarize and evaluate the current evidence supporting the use of exercise training as a medical treatment for adult patients with NAFLD.

Recent findings: At least 150 minutes each week of moderate intensity exercise of any type can improve NAFLD, both with and without modest weight loss. Exercise training reduces hepatic steatosis and liver inflammation, favorably changes body composition, improves vascular endothelial function, increases cardiorespiratory fitness and can lead to histologic response. To date, exercise-based NAFLD trials are limited by small sample size and significant heterogeneity.

Summary: While several key questions remain unanswered, exercise training will always be an important part of the medical management of patients with NAFLD.

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Keywords

physical activity; lifestyle modification; cardiovascular disease; nonalcoholic steatohepatitis; fatty liver

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of global liver disease with a prevalence of 25–30% [1]. Diagnosed by radiographic evidence of hepatic steatosis (HS) and exclusion of secondary causes of HS, including significant alcohol use, NAFLD disproportionally affects persons with obesity and diabetes [2]. NAFLD can be grouped into either nonalcoholic fatty liver (NAFL), the non-progressive type, which is characterized by >5% HS and the absence of hepatocyte injury or ballooning, or nonalcoholic steatohepatitis (NASH), the progressive type where both >5% HS and hepatocyte injury or ballooning are present [3]. By 2030, the prevalence of NAFLD in the United States is predicted to increase by 21% to 101 million; an even greater increase is expected for NASH, where an increase of 63% to 27 million is expected [4].

The development of NAFLD and progression to NASH is partly due to physical inactivity. For each hour per day of sedentary behavior, the likelihood of NAFLD increases by 4% [5]. In the absence of an approved pharmacologic treatment for NAFLD and NASH, lifestyle modification, including dietary change and exercise, which is defined as a subset of physical activity that is structured and repetitive, remains the cornerstone of treatment [6]. The goal of lifestyle modification is to achieve a modest weight loss of 5–10%, the validated threshold for histologic improvement in NASH [6]. However, less than 10% of patients will achieve this amount of weight loss [7]. Over 75% of those who do lose significant weight will regain the weight in the three years following cessation of lifestyle modification [8].

Despite NAFLD patients' struggles to meet recommended weight loss amounts, there are weight-loss independent benefits of exercise training including loss of HS and gains in cardiorespiratory fitness (CRF) [9]. Current physical activity guidelines from the Department of Health and Human Services (DHHS) recommend at least 150 minutes per week of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise for all adults [10]. A recent analysis of the National Health and Nutrition Examination Survey (NHANES) database by Kim *et al* [11]. of over 5,000 subjects with NAFLD found that for each ten minutes of physical activity, overall mortality was reduced by 7%. Additionally, the American College of Sports Medicine (ACSM) recently expanded their Exercise is Medicine (EIM) initiative to include recommendations specific to patients with NAFLD.[12] The EIM NAFLD guidelines suggest two strength training sessions on non-consecutive days in addition to the amount of moderate or vigorous intensity exercise recommended by the DHHS [13].

While several key questions remain unanswered including the role of dietary modification as a complement to exercise training, the relationship between fibrosis stage and CRF, the mechanism explaining how exercise training improves NAFLD, the optimal exercise training prescription and whether or not exercise training can lead to weight-loss independent

histologic response, our aim with this systematic review is to summarize and evaluate the current evidence supporting the use of exercise training as a medical treatment for adult patients with NAFLD.

Search methods

A detailed search was conducted in collaboration with a Medical Information Consultant (AK) using indexing languages including Medical Subject Headings and free text terms for physical activity, exercise, fatty liver, NAFLD and NASH. The following databases were searched through April 2020: Cochrane Library (Ovid), Embase (Ovid) and Medline (Ovid). Several clinical trial registries were also searched including ClinicalTrials.gov. Search results were combined into an Endnote database (version X8.2, Clarivate Analytics, Philadelphia, USA) for reference management. Reference lists from identified systematic reviews and meta-analyses were screened for additional studies.

Dietary modification as a complement to exercise training

A thorough assessment of the evidence supporting dietary modification is beyond the scope of this systematic review, however, dietary modification alone can lead to improvement of NAFLD. A qualitative systematic review by Saeed *et al.*[14] of 317 subjects from six randomized controlled trials (RCTs) [15–20] evaluated the impact of dietary intervention alone. The authors found the strongest evidence for HS reduction and weight loss with the Mediterranean diet. Low-carbohydrate, low-fat or intermittent fasting diets can also lead to these benefits, albeit fewer studies have demonstrated this. In further support of a low-fat, hypocaloric diet, Yamamoto *et al.* [21] showed significant reduction in liver enzymes and inflammation in their study of 27 NAFLD subjects. In their meta-analysis of 140 NAFLD subjects from four RCTs, Katsagoni *et al.*[22] found no difference in HS, body weight, liver enzymes or metabolic parameters when comparing a low/moderate fat diet to a moderate-carbohydrate diet. A significant amount of heterogeneity and bias were encountered by both Katsagoni *et al.*[22] and Saeed *et al.*[14], which strongly limits any large-scale conclusion about dietary intervention in NAFLD. This highlights the need to standardize NAFLD dietary interventional trial design. In the same meta-analysis, Katsagoni *et al.*[22] also investigated the combination of dietary modification and exercise training. Pooling 461 subjects from six RCTs, the authors found minimal additional benefit beyond a slightly greater reduction in alanine aminotransferase (ALT) and NAFLD Activity Score (NAS). Again, heterogeneity strongly limited pooled study conclusion. Consequently, no optimal dietary regimen has been established for patents with NAFLD. The additional benefit of enacting dietary modification as a complement to exercise training also remains unclear.

Baseline cardiorespiratory fitness

Maximal oxygen uptake (VO_{2max}) is a standard measure to assess CRF. VO_{2max} uses incremental, graded exercise testing to measure maximal oxygen consumption through standardized protocols [23]. VO_{2max} is predictive of mortality in the general population. For every 10% decrease in VO_{2max}, there is a 15% increase in overall mortality[24] CRF also predicts mortality in persons with chronic disease, including NAFLD [5, 25, 26]. The HUNT

study demonstrated a 52% increased risk of all-cause mortality over a mean follow-up of 9.4 years in 15,781 NAFLD subjects with low CRF [5]. While this study has several limitations including the estimation of CRF using a prediction model rather than direct measurement with graded exercise testing[27], the findings remain highly significant and the relationship between CRF and NAFLD/NASH continues to be an intriguing research topic. It also remains unclear if CRF leads to NAFLD development and disease progression to NASH or if there are intrinsic features of NAFLD that predispose to poor CRF. Independent of body weight, NASH patients have lower CRF than the general population [28]. In fact, the majority of patients with NASH have a poor or very poor fitness level [29]. While poor fitness is ubiquitous in NASH, Austin *et al.* [30] demonstrated differences in CRF intrinsic to NAFLD in their comparison of 17 NAFLD subjects to 15 healthy controls where $VO2_{max}$ was decreased in NAFLD subjects despite preserved exercise capacity.

$VO2_{max}$ is the gold-standard to objectively measure physiologic adaptation and CRF improvement after exercise training. $VO2_{max}$ testing is most often utilized in aerobic training studies. Importantly, improvements in $VO2_{max}$ are strongly associated with reduction in HS both in the presence and absence of significant weight loss [31, 32]. Given this relationship, it is not unreasonable to assert that $VO2_{max}$ can be used as a biomarker of not only exercise response, but also severity of HS. Whether or not $VO2_{max}$ is also related to fibrosis stage in NASH or histologic response following exercise remains unknown and poses an interesting avenue for future investigation.

Mechanism of benefit

The exact mechanism explaining how exercise improves NAFLD is undetermined, however, activation of lipolysis, upregulation of uncoupling protein-1 and adipocyte stimulating peroxisome proliferator-activated receptor gamma (*PPARγ*), as well as changes in adipocytokines all may play a role [33–37]. The AMP-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1) pathway may also be involved [38]. AMPK is a fuel-sensing enzyme that is activated by energy stress. mTORC1 is a nutrient sensor that regulates the cell cycle and protein synthesis. In healthy persons, exercise training activates AMPK and suppresses mTORC1 [39–41], leading to favorable changes in energy balance [39, 42]. In patients with NASH, AMPK activity is low and mTORC1 activity is high [42]. Animal models of obesity [43, 44] and NASH [45] have demonstrated that chronic aerobic training can upregulate AMPK and downregulate mTORC1. In patients with NASH, the effect of exercise training leads to favorable changes in downstream targets of the AMPK/mTORC1, including serum Fibroblast Growth Factor 21 (FGF21) and hepatic ribosomal protein S6 [38].

Exercise training prescription

Modality of exercise

The majority of NAFLD exercise studies utilize aerobic training. Aerobic training is defined as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature [46]. NAFLD trials have used cross-training, cycling, rowing, running, walking and other rhythmic exercise for aerobic training. Physiologic adaptation to aerobic

training is readily and reliably measured by $VO2_{max}$ testing. Resistance training has also been studied in patients with NAFLD, however, due to significant heterogeneity in exercise prescription (e.g., a muscular endurance protocol which focuses on Type I slow-twitch muscle fibers and the aerobic energy system vs. a muscular hypertrophy protocol which focuses on gains in muscle mass, Type II fast-twitch fibers and the creatine-phosphate and glycolytic energy systems) as well as lack of a standardized training adaptation assessment, conclusions about its benefit are less concrete [47]. Most resistance training trials do not specify the intent of their training program and whether or not they employ muscular hypertrophy or muscular endurance protocols, however, they typically include progressive exercise where resistance weight is increased as fitness increases. In their meta-analysis of 951 NAFLD subjects without diabetes from nine RCTs, Wang *et al.* [48] found minimal difference when comparing the impact of aerobic versus resistance training on liver enzymes, metabolic parameters and HS. Only one study was included in their analysis[49] that examined a combination of aerobic plus resistance training, limiting conclusions about both modalities together. Despite this, it is reasonable to presume that a combination of aerobic plus resistance training may lead to a greater response in more patients with NAFLD than with either modality of training alone as this has been shown in persons with obesity [50, 51].

Yoga, tai-chi, and Pilates offer alternative modalities of exercise beyond traditional aerobic or strength training. Singh *et al.*[52] randomized 37 women with metabolic syndrome and pre-diabetes to either a regular yoga practice group or non-yoga practice group. Following three months of the Diabetic Yoga Protocol, hemoglobin A1c and total cholesterol were significantly reduced when compared to the non-practicing control group. Additionally, the yoga group had a trend towards liver size reduction, and although HS was not reported, it can be inferred that a reduction in liver size may be due to loss of HS, indicating an additional benefit of yoga in patients at risk for or with undiagnosed NAFLD. Keymasi *et al.* [53] examined an 8-week Pilates training program in 10 men with NAFLD and compared them to 10 men without NAFLD. The authors found a significant reduction in body weight, body fat, liver enzymes and HS when the Pilates group was compared to the control group. We are unaware of any studies examining the benefit of tai-chi in patients with NAFLD, but, extrapolating from studies in patients with pre-diabetes or diabetes where BMI, glucose control and insulin resistance were improved following as little as 12-weeks of tai-chi [54], it is not unreasonable to think tai-chi could lead to similar improvement in patients with NAFLD.

Because multiple large comparative effectiveness studies demonstrate equivalency between exercise modalities, it is most important to consider patient compliance with exercise training and how likely they are to achieve a specific outcome when choosing a modality of exercise to prescribe. For these reasons, current guidelines from both the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of Liver (EASL) do not specify one modality over another and aerobic training, resistance training, high intensity interval training (HIIT), yoga, tai-chi, Pilates or any combination of the aforementioned can be considered when developing an individual exercise prescription.

Intensity of exercise

Low, moderate, and high- (vigorous) intensity exercise are defined by different metabolic equivalents (METs). Low intensity exercise is performed from 2.0 to 2.9 METs, moderate-intensity 3.0 to 5.9, and ≥ 6 for high-intensity [46]. HIIT is a method of exercise training that incorporates both strength and aerobic exercise with extreme intensity variation across low, moderate and high-intensities. As it is time-efficient, it is an attractive program for patients with NAFLD who have identified time constraints as a barrier to exercise participation. Hallsworth *et al.*[55] randomized 29 NAFLD subjects to 12-weeks of HIIT completed on a cycle ergometer versus standard of care and found significant reductions in HS (−3% vs. 0%, p=0.019) in parallel with improvement in cardiac function. Only one subject discontinued the HIIT intervention. Abdelbasset *et al.*[56] randomized 47 obese, diabetic NAFLD subjects to either 8-weeks of cycle ergometer HIIT, moderate intensity continuous (MIC) aerobic training or a control group. Both the HIIT and MIC groups had a significant reduction in HS (−2.3% HIIT vs. −2.4% MIC) while the control group did not show any change. Importantly, all 16 subjects in the HIIT group completed the study demonstrating feasibility of this more intensive training program, which has been criticized over a theoretical increased risk of physical injury and adverse events. Nath *et al.*[57] studied 37 subjects with NAFLD and compared low-intensity to moderate-intensity aerobic training over six months. The authors found significant reductions in BMI, total cholesterol and liver enzymes in the moderate-intensity group only. HS regressed in 66.7% of moderate-intensity subjects compared to 26.3% of low-intensity subjects. Zhang *et al.*[58] compared moderate-intensity to vigorous-intensity aerobic training in 146 NAFLD subjects and found similar benefits when comparing the two groups. At this point in time, moderate-intensity is to be recommended over low-intensity exercise training, however, a recommendation suggesting moderate-intensity exercise over vigorous-intensity exercise or HIIT cannot be made from the available evidence.

Frequency and duration of exercise training

The optimal frequency and duration of exercise training has not been established specific to NAFLD patients. Extrapolating from widely validated and evidence-based guidelines from DHHS and the ACSM, at least 150 minutes each week can be recommended [6, 59]. In terms of duration, not surprisingly, a longer duration of exercise leads to better outcomes. Regular physical activity for more than four months significantly improves metabolic parameters in NAFLD more so than if activity is discontinued before four months [48].

Clinical benefits of exercise training

Exercise training leads to many important benefits in patients with NAFLD, including a reduction in HS and liver inflammation, favorable change in body composition, improved vascular endothelial function, greater CRF and histologic response when it leads to modest weight loss (Figure 1).

Liver enzymes and inflammation

A randomized controlled study by Houghton *et al.* [60], investigated the effect of a 12-week weight neutral combined aerobic and strength training program on intrahepatic triglyceride

(IHTG), non-invasive biomarkers of fibrosis (e.g., cytokeratin-18), and inflammatory markers (e.g., interleukin-6, tumor necrosis factor α, and high-sensitivity C reactive protein) in patients with biopsy-confirmed NASH. The authors found significant improvement in IHTG, visceral adipose tissue (VAT), and plasma triglycerides, but found no improvement in liver enzymes, pro-inflammatory markers or biomarkers of fibrosis [60]. A meta-analysis by Wang *et al.* [48] of nine RCTs [9, 49, 58, 61–66] across 951 NAFLD subjects without diabetes found that aerobic training was effective in improving aspartate aminotransferase (AST) (SMD −0.26, 95% CI: −0.43 to −0.10) and reducing homeostasis model assessment of insulin resistance (SMD = −0.42, 95% CI: −0.63 to −0.22), but not significantly beneficial in improving other liver enzymes or serum lipid levels.

Hepatic steatosis

Multiple studies have examined exercise-induced changes in HS. Sullivan *et al.*[9] conducted a small RCT of 18 subjects with biopsy-proven NASH following physical activity guidelines from DHHS and found HS was reduced by 10% after 16-weeks of exercise training without weight loss compared to a 2% HS gain in the control group who received standard NAFLD counseling [9]. Interestingly, Zhang *et al.*[58] demonstrated significant reduction in IHTG was more dependent on weight loss (3%−6% total body weight), rather than intensity of exercise as they found similar benefits when comparing 73 subjects who underwent vigorous aerobic training and compared them to 73 subjects completing moderate-intensity aerobic training.

Sargeant *et al.*[67] performed a meta-analysis of 17 exercise studies (10 RCTs) with 373 NAFLD subjects. The interventions ranged from 1–24 weeks of structured exercise (aerobic training, resistance training or HIIT). The authors confirmed reduction of IHTG content was independent of weight change (−2.2%, 95% CI: −2.9 to −1.4%) but when significant weight change occurred, the benefit was strengthened (−4.9%, 95% CI −6.6 to −3.1%). Similar findings were presented by the large-scale, pragmatic Look AHEAD Trial which evaluated 5,145 subjects with NAFLD and diabetes who underwent either intensive lifestyle modification (hypocaloric diet and 175 minutes per week of moderate-intensity physical activity) or diabetic support with education only.[68] Within the intensive lifestyle group, a 2.3% reduction in HS was observed, compared to 1.1% in the diabetic support with education only group (p=0.04) [68].

Liver histology

Histologic improvement in NAFLD and NASH is a top research priority for Phase IIb/III clinical trials.[69] The NASH Clinical Research Network (NASH CRN) Histologic Scoring System includes criteria for scoring key features of NAFLD including steatosis, inflammation, ballooning, and fibrosis [70]. NAFLD activity score (NAS) is a summary score that includes steatosis (0–3), lobular inflammation (0–3) and ballooning (0–2) [70]. The two accepted histologic endpoints in NASH clinical trials are either a 2-point improvement in NAS (with at least one point derived from improvement in lobular inflammation or ballooning) or NASH resolution, defined as absence of ballooning with 0–1 lobular inflammation and no worsening of fibrosis [69, 71].

Promrat *et al.*[72] performed a RCT of 31 subjects with biopsy-proven NASH. The authors implemented 48-weeks of lifestyle intervention modeled after the Diabetes Prevention Program that included both unsupervised aerobic training for 200 minutes per week and a hypocaloric low-fat diet with regular behavioral counseling. The lifestyle group lost 8.7kg vs. 0.5kg loss in the control group ($p<0.01$). Forty percent of subjects achieved at least 10% weight loss, all of whom were in the lifestyle group. Liver histology, defined as a composite endpoint of either NAS reduction ≥3-points or NAS ≤2 post treatment, could be improved in 72% of subjects in the lifestyle group compared to 30% in the control group ($p=0.03$). This effect was driven largely by weight loss. Subjects who lost ≥7% body weight, independent of study group, had NAS reduction of 3.5 vs 1.2 in those who lost <7% body weight ($p<0.01$). While the authors concluded no significant improvement in fibrosis stage was found, there was a trend towards significance in subjects with ≥ 7% weight loss ($p=0.10$).

Vilar-Gomez *et al.* [73] also demonstrated histologic improvement in an uncontrolled trial of 293 subjects with NASH following an intensive 52-week lifestyle intervention that included both a low-fat hypocaloric diet with supervised dietary counseling every eight weeks and unsupervised 200 minutes per week of walking. Mean weight loss at 52 weeks was modest (−4.6 kg +/− 3.2kg). Thirty percent of subjects lost significant body weight independent of obesity or diabetes. Only 25% of subjects met the primary endpoint of NASH resolution and 47% had histologic improvement with NAS reduction ≥2-points without fibrosis worsening. When subgroup analysis was performed comparing those who lost ≥ 5% body weight (n=88) to subjects with <5% weight loss (n=205), both NASH resolution (58% vs. 10%, $p<0.01$) and histologic improvement (82% vs. 32%, $p<0.01$) occurred more often in subjects who lost at least 5% of their body weight. No differences were seen for fibrosis regression, defined as at least 1-stage improvement, (20% vs. 16%, $p=0.18$) at this 5% weight loss cutoff. When examining the 29 subjects with at least 10% weight loss, NASH resolution increased to 90% and 45% experienced fibrosis regression (81% when limiting to the 16 subjects with baseline fibrosis), however, several limitations of this study are worth noting. Most importantly, the majority of the cohort had very early stage NASH. Sixty-one percent did not have fibrosis on biopsy and 40% had NAS <5, significantly limiting the authors' investigations and conclusions about histologic improvement and tempering clinical expectations. We are unaware of any study investigating weight-loss independent improvement in liver histology following exercise training which is a highly significant given the inability of most NAFLD patients lose weight.

Cardiovascular disease

Cardiovascular disease (CVD) is the most common cause of death in patients with NAFLD and NASH [1, 6, 74]. Endothelial dysfunction is a validated predictor of CVD. Endothelial dysfunction leads to abnormal blood flow and development of an arterial plaque with a fibrous cap, lipid core, and *de novo* atherosclerosis. Over time, this stable plaque progresses, leading to intimal narrowing. If uncorrected, this may become an unstable plaque at risk of rupture and arterial thrombosis, leading to myocardial infarction, stroke and/or sudden cardiac death [75, 76]. Flow-mediated dilation (FMD) of the brachial artery is an effective, non-invasive measure of endothelial function [77]. A recent meta-analysis by Inaba *et al.* [78] of 5,547 subjects found that after adjusting for confounding factors, for each 1%

decrease in brachial FMD, there was a 13% increased risk of major adverse CV events [78]. Independent of traditional obesity, insulin resistance and VAT, endothelial dysfunction is found globally in NAFLD [32, 62, 79–81] and is directly related to the grade of HS [80].

Endothelial dysfunction and vascular stiffness can be improved by exercise training in patients with NAFLD. In a study of 21 NAFLD subjects, Pugh *et al.*[61] found a 16-week exercise protocol increased cutaneous nitric oxide (NO)-mediated vasodilator function, a marker of endothelial dysfunction. The improvement in endothelial dysfunction was seen in parallel with gains in $VO2_{max}$ (+10.1 mL/kg/min, 95% CI: 5.0 to 15.3) in the exercise group compared to the standard of care group (−0.9 mL/kg/min, 95% CI: −6.5 to 4.8, p=0.01). Pugh *et al.* [62] continued their evaluation with a RCT of 54 subjects with NAFLD and obesity. They found significant brachial artery FMD improvement (3.6%, 95% CI: 1.6 to 5.7, p=0.002) after a 16-week moderate-intensity exercise intervention, a change that was not sustained when measured 12-months after stopping exercise training [32].

Body composition

There is conflicting evidence about whether or not body composition changes after exercise training in patients with NAFLD. Houghton *et al.*[60] randomized 24 subjects with NAFLD to 12-weeks of aerobic and resistance training versus a weight-neutral control group. The authors found a VAT reduction of $22cm^2$ compared to an increase of $14cm^2$ in the control group ($p<0.05$). There was a trend towards reduction of subcutaneous adipose tissue (SAT) as well, albeit one that was not statistically significant. Lean body mass also significantly increased by 2kg after exercise and remained unchanged in the control group. Importantly, reduction in VAT was strongly correlated with reduction in IHTG. VAT is directly related to liver inflammation and fibrosis, independent of other metabolic risk factors including insulin resistance, and may contribute to liver disease progression through synthesis and release of inflammatory cytokines and adipokines which lead to further HS, inflammation and insulin resistance [82, 83].

Others, including Hallsworth *et al.*[84] and Oh *et al.*[85], did not find significant changes in either VAT or SAT following 8–12 weeks of resistance training, MICT or HIIT. Oh *et al.*[*85*] did demonstrate significant gains in lean mass of 1.5kg in the resistance training group and 0.6kg in the HIIT group. This study was limited by including only male subjects as sex-based differences in body composition are well described [86] and it is accepted than men have more lean mass and women more fat mass. However, sex-based differences in exercise response and reduction in adipose tissue have not been demonstrated [87] in overweight and obese persons. To our knowledge, sex-based differences in exercise response have not been investigated in NAFLD patients [88].

Conclusions

NAFLD is a leading cause of global liver disease. Prevalence rates of NAFLD are expected to increase substantially in the coming decades. Pharmacologic treatments are ineffective and have a strong side effect profile, placing increased importance on exercise as a treatment for NAFLD. Lifestyle change, centering around exercise training, remains the cornerstone for NAFLD treatment. At least 150 minutes each week of moderate-intensity exercise of any

type can lead to clinically meaningful improvements in NAFLD, both with and without modest weight loss. Exercise training leads to many important benefits in patients with NAFLD including a reduction in HS and liver inflammation, favorable change in body composition, improved endothelial function, greater CRF and histologic response if 5–10% weight loss is achieved. While several key questions remain unanswered, exercise training will always be an important part of the medical management of patients with NAFLD, even if an effective pharmacologic therapy is developed in the future.

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Abbreviations:

AASLD	American Association for the Study of Liver Disease
ACSM	American College of Sports Medicine
ALT	Alanine aminotransferase
AMPK	AMP-activated protein kinase
AST	Aspartate aminotransferase
BMI	Body mass index
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
DHHS	Department of Health and Human Services
EASL	European Association for the Study of Liver
EIM	Exercise is Medicine
FGF21	Fibroblast Growth Factor 21
FMD	Flow-mediated dilation
HS	Hepatic steatosis
HIIT	High intensity interval training
IHTG	Intrahepatic triglyceride
mTORC1	Mammalian target of rapamycin complex 1

VO_{2max}	Maximal oxygen uptake
METs	Metabolic equivalents
MIC	Moderate intensity continuous
NHANES	National Health and Nutrition Examination Survey
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
NASH CRN	NASH Clinical Research Network
NO	Nitric oxide
PPARγ	Peroxisome proliferator-activated receptor gamma
^{1}H-MRS	Proton magnetic resonance spectroscopy
RCT	Randomized controlled trials
SAT	Subcutaneous adipose tissue
VAT	Visceral adipose tissue

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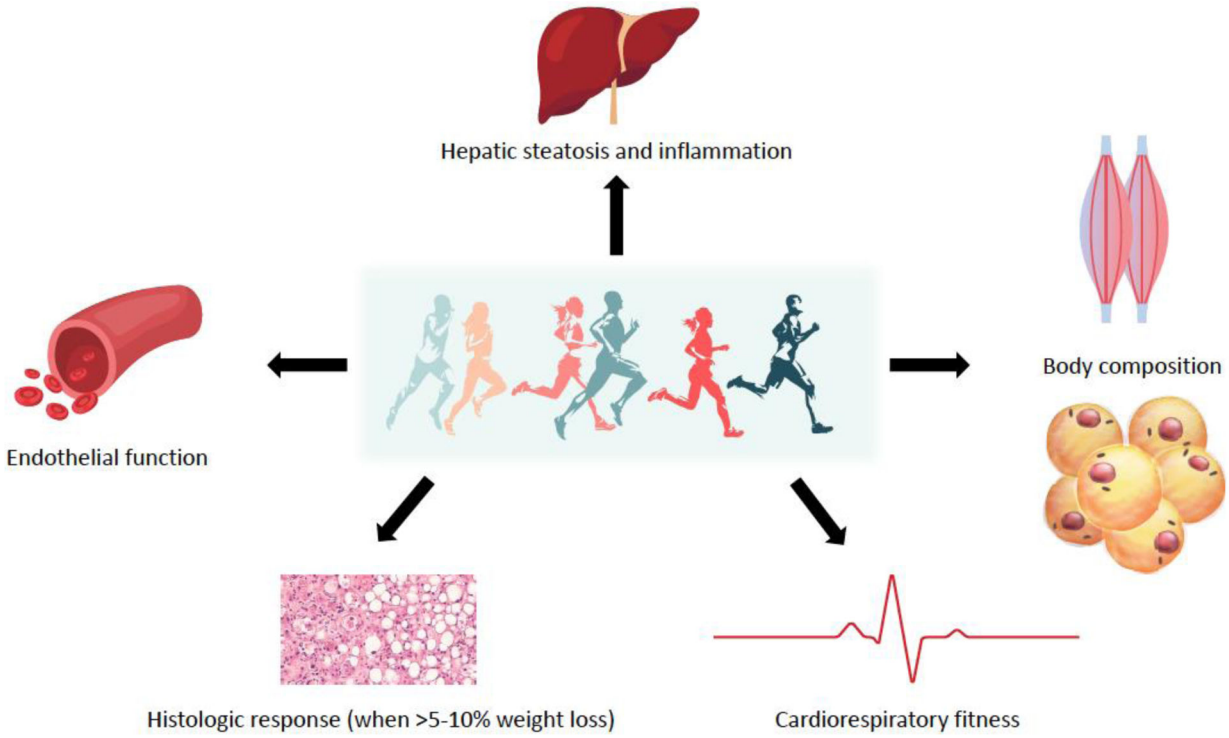

Figure 1.
Benefits of exercise training in patients with NAFLD