

Non-Alcoholic Fatty Liver Disease and Different Protocols of Physical Exercise: A Mini Review

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ABSTRACT

In recent years, non-alcoholic fatty liver disease (NAFLD) has emerged as a cause of chronic liver disease that may lead to severe clinical situations, which include cirrhosis and hepatocellular carcinoma. Some pathophysiological processes contribute to the deposition of intrahepatic lipids, inflammation, and fibrosis. Lifestyle modifications that include regular physical exercise (RPE) potentially benefit in the treatment and have a preventive measure of this condition. It is

not very clear by what mechanisms the RPE can modulate NAFLD. Experimental and human studies with RPE have demonstrated benefits related to weight loss, improvement of lipogenic profile, inflammatory response and histological features; however, aspects as type (aerobic or resistance), intensity and ideal frequency remain unclear. The objective of this review is to describe the current knowledge of different types of physical exercise covering their effects and mechanisms in NAFLD.

Key words: Physical Exercise; Aerobic Exercise; Resistance Exercise and Non-Alcoholic Fatty Liver Disease

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INTRODUCTION

In recent years, non-alcoholic fatty liver disease (NAFLD) has emerged as a significant cause of chronic liver disease, having a prevalence of approximately 30% in adults with normal weight and about 90% in the obese population^[1]. NAFLD is one of the most important cause of liver-related morbidity and mortality, being responsible for the significant increase in the rate of liver transplant around the world^[2,3,4]. NAFLD consists of a wide spectrum of diseases from non-alcoholic fatty liver, to non-alcoholic steatohepatitis (NASH), which is characterized by hepatic fat deposition with inflammation, micro and macrovesicular steatosis, hepatocellular ballooning and hepatic fibrosis. In the most advanced cases, it may lead to cirrhosis and hepatocellular carcinoma^[4].

It is known that lifestyle modifications as dietary habits and increased physical exercise (PE) are recommended to prevent and to

treat NAFLD. It has been described that PE induces increases cardio-respiratory fitness and decreases intrahepatic lipid storage, resulting in an improved health condition. The objective of this review is to describe the current knowledge of PE to prevent and to treat NAFLD and mechanisms involved.

PATHOGENESIS OF NAFLD

The world population is living a moment of nutritional transition. The high availability of industrialized foods at affordable prices, exaggerated stimulus of consumption high fat diet, and anxiogenic food rhythm, allied to sedentary behaviors with a reduction in the practice of physical exercise, are determining factors for the increase in the rate of overweight and obese individuals in the current contemporary setting. The development of NAFLD can occur due to the imbalance in carbohydrate (CHO) and saturated lipids intake, which activates the lipogenic pathway, which leads to the production of an inflammatory response capable of producing ROS, hepatic stellate cell activation and fibrosis. Furthermore, NAFLD is associated with obesity and insulin resistance (IR) due to the production of free fatty acids (FFA) in greater proportion^[5]. This FFA availability associated with a decrease in the lipid oxidation rate leads to a greater intrahepatic lipid storage, contributing to the aggression in hepatocytes and progression of this disease^[11].

The inflammatory response and the production of reactive oxygen species characterize the multiple hits theory, in which it refers to actions that compromise liver function^[6]. The exacerbated production of FFA attenuates mitochondrial reactions, such as beta-oxidation and oxidative phosphorylation. These factors compromise mitochondrial activity, which in turn changes the production of intrahepatic adenosine triphosphate, generating an inflammatory response in the hepatocyte parenchyma, triggering the propagation of ROS^[7].

When exposed to these factors, the cellular machinery responds with higher production of pro-inflammatory cytokines, leading to activation of multiple aggressions to the liver. Therefore, the progression of these clinical conditions and decompensation of liver function contribute directly to the establishment of NAFLD and, subsequently, to the development of fibrosis, cirrhosis and hepatocellular carcinoma^[7,8,9].

Benefits of physical exercise

Sedentary behavior and unhealthy eating habits contribute to an increase in the incidence of chronic metabolic disorders such as cardiovascular disease (CVD) and insulin resistance. Therefore, it is fundamental for the individual to maintain a regular practice of PE under appropriate conditions. Through the contraction of large muscle

groups, the benefits generated by the PE result in an increased oxidative rate of FFA, which improves the phenotype of NAFLD. In addition, it occurs an immunomodulation of inflammatory factors, contributing to a positive balance in the inflammatory process. The improvement and maintenance of this positive balance is fundamental for the regression of NAFLD since the inflammatory response associated with the production of ROS and hepatic fibrosis^[10].

Muscle activation, especially the large groups, leads to an increase in energy expenditure, causing improvements in mitochondrial reactions. These reactions are fundamental to prevent NAFLD and avoid further complications^[11]. When mitochondrial beta-oxidation levels are increased, intrahepatic triglycerides are hydrolyzed in FFA and sent to the bloodstream. Then FFAs are used by muscles as an energy source during PE. In long-term physical activities, the oxidative pathway is predominantly used, and fat is the primary energy source for muscle activation. This process is regulated by the peroxisomal proliferation factor activated by gamma co-activator alpha (PGC-1 α) pathway and respiratory nuclear factors (NRF-1, NRF-2). In the aerobic PE, these proteins stimulate a series of metabolic reactions, providing an increase in mitochondrial functionality, such as increased beta-oxidation and oxidative phosphorylation^[12].

CVD and metabolic syndrome appear as contributing factors for the worsening of the clinical conditions of NAFLD patients. It is currently seen that there is an increase in the pharmacological interventions for the treatment of metabolic syndrome and CVD; however, regular physical exercise and body weight reduction remains as the main target to reverse NAFLD. These PE benefits can improve the quality of life, especially in the obese population^[13,14].

The recommendation for practice of physical exercise is at least a total of 150 minutes of PE at moderate intensity and frequency of 3 times weekly or 75 minutes of PE in vigorous intensity and frequency of 2 times a week, according to the American College of Sports Medicine. Generally, the individual affected by NAFLD has reduced cardiorespiratory capacity and a lower rate of lipid oxidation, which may cause more significant progression in NAFLD. The increase in PE leads to a better cardiorespiratory capacity, improvement in bone density, mitochondrial activity, and lipids oxidation^[15]. Regarding resistance exercise regarding maintenance of muscle mass levels in healthy adults, ACSM recommends that a frequency of at least two days per week be given a moderate to vigorous-intensity with a pattern of 8-12 repetitions per exercise series^[15].

AEROBIC PE

The regular practice of PE can generate several benefits in the health and quality of life of people with NAFLD (Table 1). It is recom-

Table 1 Studies with physical activity and exercise in NAFLD in humans.

| Study | Sample | Mean Age | Exercise Type | Liver Benefits | General Benefits |
|--|--------|----------------|------------------|--|---|
| Kistler <i>et al</i> ^[11] 2015 | 813 | 48 | UF | Vigorous exercise declined NASH conditions and advanced risk fibrosis | Insulin resistance decreased in vigorous exercise group |
| Oh <i>et al</i> ^[26] 2014 | 218 | 47.7 - 53.9 | Aerobic Exercise | Improvement in hepatic steatosis activity and fibrosis | Improvement in HOMA-IR and apoptotic markers |
| Tsunoda <i>et al</i> ^[19] 2006 | 1149 | 52.1 \pm 9.9 | Aerobic Exercise | Improvement in biochemical profile | UF |
| Fearly <i>et al</i> ^[27] 2012 | 13 | 58 \pm 3 | Aerobic Exercise | Improvement in AST, ALT and decreased intrahepatic lipids | Decreased CK18 markers and decreased FAS ligand |
| Gonçalves <i>et al</i> ^[9] 2013 | | UF | Aerobic Exercise | Reduction of ROS and prevention of degeneration of intrahepatic mitochondria | |
| Shida <i>et al</i> ^[34] 2017 | 61 | 45.9 - 53.1 | UF | Reduction of hepatic stiffness and hepatic lipid content | Exercise improved Kupffer cells' function and better immune system functionality |
| Rezende <i>et al</i> ^[35] 2016 | 40 | 55 | Aerobic Exercise | No improvement in hepatic steatosis | Postmenopausal women showed improvement in waist circumference, high-density lipoprotein cholesterol, and cardiopulmonary performance |

UF: Uninformed.

mended for the patient to perform physical exercises regularly; however, different types of physical activities can generate different effects on NAFLD. Therefore, it is important to understand how the variables related to physical training, such as intensity, duration, and frequency, can improve the clinical profile of these patients^[23,24,25]. Aerobic exercise is the most type of physical exercise practiced. One of the key features of aerobic exercise is the increased intake of oxygen in the body. In terms of motor performance, aerobic exercises are continuous and prolonged. Some examples of aerobic exercises are running, cycling, swimming and walking. Another characteristic of aerobic exercise is the use of lipids as an energy substrate during their practice, in the oxidative pathway^[25].

A study with 1149 Japanese patients with NAFLD demonstrated that those who regularly exercised at moderate intensity had better values in the biochemical variables and prevented the progression of NASH (Table 1). In addition, an association was found between the time spent in physical exercise per week and the incidence of NAFLD. Furthermore, the regular practice of physical exercise has been an important factor for the improvement of the general health of patients^[18,26].

Rezende *et al.* demonstrated that 24 weeks of aerobic exercise was able to attenuate hepatic steatosis in menopausal women with excess intrahepatic fat; however, this method did not reduce the production of pro-inflammatory cytokines in these patients^[22].

In Rabøl's study, a physical training protocol was performed between 75-85% of maximal heart rate and duration of 12 weeks. In their results, an improvement in intrahepatic triglyceride levels, a decrease in insulin resistance, and decrease in *de novo* lipogenesis was observed after a single PE session^[27].

The study conducted by Oh *et al.*^[17] demonstrated that walking as a physical activity practice, performed at 240 minutes per week, decreased hepatic stiffness modulating the fibrogenic profile of patients with NAFLD (Table 1). These benefits generated by the regular practice of physical exercise, generate an increase in the basal metabolic rate, increasing in the FFA oxidative rate, directly contributing to improving parameters in hepatic metabolism in NAFLD.

A study conducted by Tsunoda and co-authors (Table 1) showed that, vigorous physical activity (VPA) (≥ 7 METs of BP) was able to decrease the incidence rate of NASH in people with hepatic steatosis. In contrast whereas moderate low-physical activity (MLPA) (3-5 METs) and moderate high-physical activity (MHPA) (5-7 METs) had no effect on progression to NASH. To confirm this finding, a multivariate-adjusted Cox model showed a significant preventative effect of VPA on progression to NASH (HR = 0.55, 95% CI = 0.32-0.94)

and there were no significant associations between MLPA (HR = 1.01, 95% CI = 0.79-1.30) or MHPA (HR = 0.97, 95% CI = 0.66-1.42) and progression to NASH. Based on these findings, exposure to increased physical activity intensity appears to be a beneficial and essential factor for NASH management^[18].

Fearly *et al.*^[17] (Table 2) performed an aerobic exercise protocol for 7 consecutive days at a frequency of 2 times per week and aduration of 60 minutes per session at a vigorous intensity. It was found that independently of body weight loss, obese individuals previously sedentary with NAFLD submitted to this aerobic exercise protocol were able to significantly decreased plasma levels of cytokeratin caspase cleavage marker of intermediate filament 18 (CK18) which is associated with the hepatic fibrosis process. In addition, evidence has been found that reductions in apoptosis may be related to reductions in fatty acids synthesis ligand (FasL), possibly resulting from improvements in oxidative capacity. The mechanisms associated with RPA and hepatic fibrosis remains unknown, but it is believed that the regular practice of physical exercise in moderate to vigorous intensities acts as an immunomodulatory tool in the decrease of fibrogenesis, among other factors linked to the pathogenesis of NAFLD.

Some difficulties in interventional studies with humans are observed, such as the adoption of a healthier lifestyle, lack of adherence to health promotion programs, commitment of participants and/or professionals, poor quality of the structure or absence of reference centers for the regular practice of physical activities are some examples^[30,32,33]. An alternative but efficient way to overcome such difficulties is the use of animal models' studies (Table 2). Among the animal models, obese mice (ob/ob) have been widely used because of their physiological and genetic characteristics. This animal model becomes obese in an early stage of life, hyperphagic, present hyperinsulinemia, and hyperglycemia^[34,35]. Although ob/ob mice are not the best representative model of the etiology of obesity in humans, its main characteristic of leptin deficiency has caused an interest for more precise investigations and the creation of new research fields such as hormonal regulation, metabolic transition and obesity phenotype.

In a previous study with ob/ob mice, PE improved the anti-inflammatory response and decreased the production of inflammatory cytokines. When activated, the inflammatory pathway increases hepatic damage and its homeostasis. Despite the fact that animals had not lost weight significantly, the authors confirmed positive changes caused by PE in parameters such as intrahepatic lipids, sensitivity and insulin resistance. However, they affirmed that when PE causes weight loss, the benefits are double improved (Table 2)^[29].

Table 2 Interventional studies with physical activity and NAFLD in animal model.

| Study | Sample | Animal Model | Exercise Type | Liver Benefits | General Benefits |
|--|--------|--------------|------------------|---|---|
| Evangelista <i>et al.</i> ^[28] 2015 | 17 | ob/ob | Aerobic Exercise | Positive effect on body weight control but not in the liver steatosis in a leptin deficiency model. | Exercise prevented body weight gain |
| Macpherson <i>et al.</i> ^[20] 2015 | 27 | C57BL/6 | Aerobic Exercise | UF | Induced-exercise increases IL- 6, IL-10 and reduced, macrophages M1 rates |
| Haczeyni <i>et al.</i> ^[22] 2015 | 8 | Wistar | Aerobic Exercise | Exercise improves function, liver inflammation and ameliorates Fatty Liver Disease in obese diabetic mice | Exercise generated protective effects of metabolic function in atherogenic hyperphagic mice fed, preventing the early onset of obesity and diabetes, in association with increased muscle insulin sensitivity and improved adipose morphometry. |
| Wisløff <i>et al.</i> ^[36] 2005 | UF | N:NIH rats | Aerobic Exercise | Physical exercise reduced the susceptibility in C57BL6 trained mice. | Trained mice showed higher cardiorespiratory capacity and better mitochondrialfunction |
| Alex <i>et al.</i> ^[23] 2016 | 24 | C57BL/6 | Aerobic Exercise | Physical exercise reduced liver steatosis in C57BL6 trained mice | Trained mice showed higher cardiorespiratory capacity and better oxidative capacity |

UF: Uninformed.

Evangelista *et al.*^[28] performed an aerobic PE protocol with moderate intensity (60% of the maximum velocity), 60 minutes per day and five days per week in ob/ob mice. In their results, it was verified that the exercise had a positive effect on body weight and energy expenditure; however, no significant changes in hepatic steatosis activity (NAS score) were observed in comparison to the sedentary group (Table 2).

Rector^[26] and co-authors, evaluated in C57BL6 animals with different levels of aerobic capacity linked to the development and severity of NAFLD (Table 2). The results showed that after 25 weeks of aerobic exercise, the trained group obtained less susceptibility to NAFLD, less mitochondrial damage and better histopathological conditions. Such findings can be explained by the increase in mitochondrial biogenesis and its oxidative reactions, generating a greater beta-oxidation of the intrahepatic lipids. In addition, Morris *et al.*^[25] demonstrated in animals with NASH that the mitochondria also underwent morphological changes. This phenomenon compromises liver function, increasing its lipid storage capacity and causing inflammatory activity, leading to an increase in clinical progression and disease severity.

RESISTANT PE

Concerning resistance exercise, it is characterized as short duration and high intensity exercise. It has as main benefits increase of muscular strength, a decrease of body fat, increases and maintenance of skeletal muscle. In terms of energy source, resistance exercise makes priority use of carbohydrates for maintenance and functionality. Due to its fast contraction characteristics, two energy routes are used to supply the physical activities performed: creatine phosphate (CP) and the glycolytic pathway. The CP is a route that provides fast energy supply; however, the use of this energy substrate lasts on average 0-5 seconds. Therefore, during the practice of physical exercise, the glycolytic pathway is used to produce ATP^[25,36].

In terms of energy substrate, aerobic exercise seems to be the most adequate, due to the predominant use of lipids to generate ATP however, the regular practice of resistance exercises should be encouraged. A review by Loomba and Cortez Pintodemonstrated that resistance exercise has great importance in the prevention and control of NAFLD. This type of exercise provides greater control in insulin signaling in patients with NAFLD^[37].

Insulin regulation is essential to avoid a higher level of hepatic lipogenesis, because in the condition of insulin resistance, stimulating factors of lipid production have their expression increased and this deflagrates pro-inflammatory stimuli capable of maximizing severe hepatic lesions with the possibility of progression the clinical staging of these patients. Among these factors, we highlight Sterol regulatory element binding protein 1 (SREBP1C) fatty acids synthesis (FAS), responsible for lipogenesis in response to lower levels of skeletal muscle activity during physical activity^[34]. A recent study by Shida *et al.*^[21] demonstrated that patients with NAFLD had lower muscle mass in various body segments (Table 1). This level of muscle mass was related to susceptibility to NAFLD and such an explanation can be given, because by increasing the mass level, the skeletal muscles acquire a higher metabolic capacity and lower lipids in muscle and liver^[22]. More studies are needed evaluating the regular practice of resistance exercises to better understand the main mechanisms and how this type of exercise can improve the quality of health in patients with NAFLD.

CONCLUSION

Regular PE practice appears as a fundamental tool in the clinical

management in different types to provide benefits in metabolic, inflammatory, neuromuscular and cardiorespiratory fitness. In this way participating the improvement in the quality of health of individuals with NAFLD.

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