What Is the Effect of Physical Exercise on NAFLD/NASH

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Abstract: Non-alcoholic fat liver disease (NAFLD) is a pathologic entity characterized by an excessive accumulation of hepatic lipid without alcohol consumption. Both endurance and strength exercise have shown to be beneficial in NAFLD. PubMed database has been searched for randomized trials and prospective cohort studies in adults aged ≥ 18, rats and mice that have investigated the effects of at least 4 weeks of exercise only or combination with diet on NAFLD from 2014 to 2019. The review selected have been those in which exercise was clearly described by type, duration, intensity, and frequency, and that the NAFLD diagnosis, as well as the outcome measures, were confirmed through, at least, one of the following methods: biopsy, anthropometric measures, blood testing, ultrasonography imaging, biochemical analysis and Image Resonance Magnetic (MRI). Lifestyle has shown to greatly influence human behavior and health, however, a major factor impacting studies results is the difficulty in controlling people`s compliance with a healthier lifestyle, unlike animals that are forced to exercise over time, frequency and intensity, according to the researchers` wish. Therefore, animal studies have shown better results of the effect of exercise on the disease. However, both human and animal studies have reached a positive change in the following parameters: weight, fat percentage, blood glucose, insulin and ALT and AST levels. Physical exercise improves non-alcoholic fat liver disease (NAFLD), however, an optimum approach is still unclear. A regular and long-term systematic practice of exercise leads to better general health, body weight control, and life quality improvement.

Keywords: Physical Exercise, NAFLD, Metabolic Syndrome, NASH

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of chronic liver disease worldwide [40]. NAFLD occurs in patients with no history of alcohol abuse, in which there is an excessive increase in fat in the liver [40]. Although the majority of NAFLD patients have the only steatosis without progression, a considerable fraction develops non-alcoholic hepatitis stasis (NASH), which can lead to fibrosis in 20 to 40% of cases, of which 10% of cases can progress to cirrhosis and 1-5% develop hepatic cell carcinoma (HCC) [39, 41]. It is estimated that about one-third of early-stage NASH cases will progress to stage 3 or 4 fibrosis (cirrhosis) over 5 to 10 years [42], also increasing the risk of mortality as fibrosis progresses for more severe stages [43].

NAFLD can be caused by interactions of environmental and genetic factors or by metabolic complications such as hyperglycemia, diabetes, dyslipidemia, metabolic syndrome, and hypoadiponectinemia, so that these are associated with the development of non-alcoholic hepatitis stasis (NASH) and liver fibrosis [40, 44]. In NASH, the factors...
physical exercise in NAFLD shows significant benefits on physical exercise has a positive impact on NASH patients’ bioactive ingredients, and the practice of regular physical activity is beneficial in NAFLD. Two interesting questions are how does exercise benefit NAFLD and what is/are the specific characteristics of vegetables proteins, carbohydrates and lipids, and also from several non-nutritional compounds such as polyphenols, phytic acid or α-galactoside oligosaccharides [13, 34].

According to Cho, J. et al. [5] show that caloric restriction solidified its potential in treating NAFLD, however, combined with physical activity resulted in a greater decrease in body and abdominal adiposity, decreased blood lipids and decreased intrahepatic fat content, together with decreased hepatic glucose production and improved insulin sensitivity. Noting that physical exercise has a very positive beneficial effect as it favors greater weight loss through negative energy balance. Therefore, if caloric restriction alone is not effective, physical exercise should be included in NAFLD treatment.

Autophagy is a cellular catabolic process that causes the degradation of the liver cell components itself, which can improve NAFLD by reversing oxidative stress and mitochondrial dysfunction that contribute to hepatocyte damage and activation of stellate cells and fibrosis decreases the accumulation of liver lipids and fibrosis in NAFLD [5, 27].

According to Al-Jiffri, O. et al. [2] postulated that there is no proven treatment for patients with NAFLD are currently available. Weight control and reduction, as well as lifestyle modifications with diet changes and increased physical activity, are generally recommended as the first step in the treatment of patients with this condition. Decreasing and maintaining weight reduction can improve NAFLD, but the results of several reports are inconsistent.

This review is intend to understand and compare the effect of physical exercise on humans and rats with NAFLD.

Studies have shown that both endurance and strength exercise are beneficial in NAFLD. Two interesting questions are how does exercise benefit NAFLD and what is/are the mediators of the muscle-liver axis whereby the muscle regulates hepatic metabolism. However, considering the scarcity of studies that suggest a definite and precise answer to these questions, further research is needed in order to widen knowledge into the mechanisms through which physical exercise has a positive impact on NASH patients’ life quality [25, 34, 38].

Therefore, the development of a prevention and treatment strategy includes changes in lifestyle, such as caloric restriction, diets with low fat and low fat and low glycemic index, and increasing consumption of foods rich in beneficial bioactive ingredients, and the practice of regular physical activity. Rosa-Caldewell et al. [13], shows that vegetables exhibit a variety effects related to their antioxidant, hypoglycemic, and hypolipidemic properties due to the specific characteristics of vegetables proteins, carbohydrates and lipids, and also from several non-nutritional compounds such as polyphenols, phytic acid or α-galactoside oligosaccharides [13, 34].

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According to Al-Jiffri, O. et al. [2], the exercise benefits the NAFLD has mainly autophagy in NAFLD. Physical exercise is a non-pharmacological intervention capable of improving liver function test in NAFLD, ensuring that physical exercise is beneficial through improved autophagy in skeletal muscle and possibly in the liver. Wang, B et al. [28], is currently looking for the mechanisms by which exercise stimulates liver autophagy. However, the beneficial of physical exercise cannot be attributed only to the stimulation of autophagy.

Physical exercise increases the secretion of hormone irisin. The moderating increase by the exercise of circulating irisin is likely strongly related to the improvement of body fat mass, insulin resistance and growth hormone. Although irisin increases with exercise, there is a tendency to decrease with exercise maintenance and the progressive loss of its benefits. One way to maintain your production is stimulation through the variation of exercises that must be accompanied by a good professional in the field. Interventions focused on monitoring the NAFLD are weighted, so physical exercise with calorie restriction provide this overall benefit. Long-term studies are needed to establish how exercise produces metabolic organ homeostasis in patients with NAFLD.

Longitudinal studies are needed to stabilize the mechanisms by which physical exercise produce homeostasis of the triad of metabolic organs in patients with NAFLD. These searchers will provide the case for optimizing physical exercise and lifestyle changes, including dietary reeducation to reverse liver and non-liver organ dysfunction, and clinical consequences in NAFLD and metabolic syndrome.

2. Study Identification and Selection

The methodology used in this review was through the selection of bibliographic research through scientific articles in the PubMed database. The search terms used to identify the articles were: ("NAFLD", "non-alcoholic fatty liver disease", "NASH" "non-alcoholic fatty liver", "fat", "fatty liver", "steatosis") and ("exercise", "aerobic training", "resistance training", "resistance training", "strength training", "diet").

Animal and human studies, adults ≥ 18 years old of any sex or ethnic origin, were investigated that investigated the effects of at least 4 weeks of exercise or combination with diet in the NAFLD published in the period 2014 to 2019.
NAFLD diagnoses and the response measures, were confirmed by at least one of the following methods: biopsy, anthropometric measurements, blood count, ultrasound, biochemical analysis and magnetic resonance imaging (MRI). Trials that included dietary interventions along with exercise were accepted if they met all criteria.

3. Evaluation of the Effect of Physical Exercise on NAFLD

Studies investigating the effect of physical exercise whether associated to diet (hypercaloric for rats and mice, and hypocaloric for humans) or not, in NAFLD/NASH subjects with insulin sensibility. The selection of the methodology of studies clearly prescribed its intervention, such as the duration, intensity and frequency of physical exercise.

Studies that did not specific exercise prescriptions, outcome measures demonstrating an exercise effect (i.e., measures of fitness and/or strength), and quantitative measures of intrahepatic fat, were not included. Moreover, studies or study arms for which dietary supplements, herbal preparations, nutraceuticals were the intervention to the study were also included. All studies performed calculations of changes in relation to the percentage of liver fat, and this reduction was compared between the groups that received exercise and those that received a diet plus physical exercise.

The revised animal studies herein yield beneficial results regarding the effect of exercise as shown table 1. Five studies Singh V, et al. [3], Batatinha HAP, et al. [9], Marcinko K, et al. [14], MacLean C, et al. [18], Shojae-Moradie F, et al. [23] have had a significant improvement of the disease with exercise, which had in their training method an intensity of 10 to 20 m/min with a frequency of 5 times a week for 40 minutes. Rosa-Caldewell, M. E et al. [23], have applied their volunteer training method with 4 weeks of intervention, getting better levels both of AST and TNF-α IL-6.

The remaining animal studies all have had beneficial results, which also have used their method similar to those of significant results, being different from those of Frantz, E. D. C et al. [28] with a frequency of 4 times a week, and Oh S, et al. [16] with 3 times a week.

Overall, the articles have presented similar methods, being different only as to the duration of the study, which has ranged from a minimum of 4 weeks to a maximum of 16 weeks. These studies have shown similar results: improvement in AST, ALT, insulin levels, glucose, TNF-α and IL-6, weight reduction and percentage fat.

Table 1. Methodology and results of the effect of physical exercise on animals.

| Author                | Method     | Results                        | Conclusion         |
|-----------------------|------------|--------------------------------|--------------------|
| KAWANISHI, N. et al.  | 34/4       | 15 – 20 m/min                  | % Fat ALT TNF-α, IL-6 | Significantly      |
| [11]                  |            | 60 min 5 x week                | TG                 |                    |
| AAMANNA, L. et al.    | 26/2       | 60% VO₂ Max. 5 x week          | % Fat ALT AST      |                    |
| [23]                  |            | 60 min 5 x week                | –                  |                    |
| BATATINHA, H. A. P.  | 12 m/min   | 12 weeks                       | % Fat Weigh ALT    |                    |
| et al., [9]           |            |                                | TG                 |                    |
| CHO, J. et al.        | 12 m/min   | 50 min 5 x week                | Mitochondrial Improvement | Beneficial   |
| GONCALVES, I. O.     | 15-25 m/min| 5 x week                       | % Fat Weigh TG     |                    |
| PASSOS, E. DIOGO, C.  |            | 60 min 5 x week                |                   |                    |
| et al. [26]           |            |                                |                   |                    |
| MIOTTO, P. M. et al.  | 16/8       | 15 m/min 45 min 4 weeks        | AST TNF-α IL-6     | Significantly      |
| [29]                  |            |                                | –                  | –                  |
| ROSA-CALDWELL, M. et al. [13] | 20/2 20 m/min 60 min | 5 x week 4 weeks | ALT TG TNF-α IL-6 | Stress oxidative | Beneficial |
| WINN, N. C. et al.    | voluntary 10 weeks | 60 min 4 x week | % Fat Weigh Glucose |                   | Beneficial |
| WINN, N. C. et al.    | voluntary 10 weeks | 60 min 4 x week | % Fat Weigh Glucose |                   | Beneficial |
| XILO, J. et al.       | voluntary 10 weeks | 60 min 5 x week | 16 weeks | Weigh Insulin AST | Alt TG | Stress Oxidative | Beneficial |
| YOSHIMURA, S. et al.  | voluntary 6 weeks | 65-80% V VO₂ Max. | ALT | % Fat ALT | Glucose TG | Beneficial |
| KAPRAVELOU, G. et al. | 80/10     | 60 min 5 x week | 8 weeks | % Fat AST ALT | Glucose TG | Beneficial |
| MOON, H. Y. et al.    | 19/2       | 10 m/min 50 min | 4 weeks | % Fat ALT | Glucose TG | Beneficial |
| HACZEYNI, F. et al.   | 32/4       | 50-75% VO₂ Max. 4 x week       | % Fat Weigh ALT Insulin |                  |                      |
| FRANTZ, E. D. C. et al. [38] | 30/10 15/20 m/min | 60 min 30 min | 12 weeks | % Fat Weigh Insulin | Glucose ALT | TNF-α IL-6 | Beneficial |

Note: TG = Total Glucose, IL-6 = Interleukin-6, TNF-α = Tumor Necrosis Factor-α, VO₂ = Oxygen Consumption, AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase.
The human studies have yielded 3 types of results as shown in table 2, significant, beneficial and those, which have shown no influence of physical exercise on the disease. Zelber-Sagi, S; Al-Jiffri, O. et al. [33, 2] have found significant improvements in ALT, AST, insulin, total cholesterol and BMI, having in their method an intensity of 40% H. R Max, and with frequency of 3 times a week and duration of 40-45 minutes each session, for three months.

Five studies have shown no improvement in the disease due to physical exercise. They have had some differences in their methods compared to those studies, which have demonstrated significant results. Oh, S. et al. [20] have applied the exercise at an intensity of 40% H. R Max, and frequency have been 3 times a week, lasting 45 to 60 minutes for three months.

Takahashi A, et al. [6] have worked with 50% of the maximum strength in bodybuilding exercises, Zelber-Sagi S et al. [15] have applied 5 sprint shots, 2 times a week, with a small number of participants, and Malin, S. K. et al. [36] used only 7 days of intervention. These non-significant results may have been due to the method applied and also to difficulties in controlling patients compliance with the training program, however Oh, S.; Croci, I. et al. [20, 6] have obtained better results in their diet groups.

In human studies, in general, the exercise sessions frequency have been 3 times a week, lasting 45 to 60 minutes and with large variations in intervention time, ranging from seven days to 16 weeks.

**Table 2. Methodology and results of the effect of physical exercise on humans.**

| Author                      | Method                  | N  | Intensity       | Session length in times | Session frequency | Time of intervention | Results that there was improvement | Conclusion    |
|-----------------------------|-------------------------|----|----------------|-------------------------|------------------|----------------------|-----------------------------------|---------------|
| MARCINKO, K. et al. [14]    | Sprint                  | 15-22 m/min 60 min 3 x week 6 weeks  | %Fat Insulin ALT       | Beneficial       |
| PASSOS, E. PEREIRA, C. D. et al. [31] | 15-25 m/min 60 min 5 x week 8 weeks | Insulin TNF-α IL-6 | Beneficial       |
| GONÇALES, I. O. et al. [37] | 15-25 m/min 60 min 5 x week 8 weeks | Weigh ALT AST TG | Significantly     |
| GONCALVES, I. O. et al. [10] | 15-25 m/min 60 min 5 x week 8 weeks | %Fat Stress Oxidative | Beneficial       |

N = number of participants, VO2 oxygen volume
In animal studies, the intensity, and frequency of the applied method have been higher than those in human studies; consequently, the results have also shown more improvement in the disease due to physical exercise. This might have been because of difficulties in changing people’s lifestyle. Therefore, considering that lifestyle greatly influences human behavior and health, a major factor impacting studies results is the difficulty in controlling people’s compliance to a healthier lifestyle, unlike animals which are forced to exercise over time, frequency and intensity, according to the researchers’ wish.

The AIT method that the author used in this study is a viable intervention technique to improve plasma and hepatic biochemical parameters as well as hepatic histological alterations inherent to early stages of NAFLD in obese Zucker rats. The training protocol was especially efficient to improve insulin sensitivity and decrease the hepatic lipid content, as well as ameliorating the oxidative stress conditions in this organ [5, 30].

Different methods and parameters have been used to analyses data in animal and human studies. Human studies have been done through anthropometric and laboratory measurements, whereas rats or their livers have been analyzed by immunohistochemical and blood tests. Animal studies have shown better results of the effect of exercise on the disease, while less significant result have been observed in humans. However, both human and animal studies have reached a positive change in the following parameters: weight, fat percentage, blood glucose, insulin and ALT and AST levels [4].

The study herein has found that a 5 times/week endurance exercise program decreases hepatic fat content and serum fibroblast growth factor 21 (FGF21) levels, without weight loss in elderly Japanese men. These evidences suggest that endurance physical exercise improves the resistance of FGF21 without weight loss and provides further clarification that exercise alone, without weight loss, has beneficial effects prevention of age-related cardio metabolic diseases [26].

Triglycerides, visceral fat and circulating HTGC in adults with NASH decreased with physical exercise, regardless of weight loss. Therefore, the intensity of the exercise must be considered in the prescription of exercise and intervention programs for NASH treatment for being effective in reducing the content of hepatic triglycerides (HTGC). Although physical exercise has a beneficial effect on HTGC and visceral fat for people with NASH, caloric restriction plays an essential role in the disease [10].

The exercise intervention in nondiabetic men with NAFLD has significantly improved both fitness and cardiometabolic health. In addition, they have shown a significant reduction in intra hepatocellular fat (IHCL), however, their liver continued to export excessive amounts of triglycerides (TGs) in very-low-density lipoprotein (VLDL). This might have been due to a failure in normalizing IHCL and restoring hepatic insulin sensitivity. Hence, a longer duration or higher-intensity exercise intervention, or an approach combined with calorie restriction might be required to achieve lower amounts of TG and VLDL exportation and to lower plasma TG and VLDL production rates [24].

### 4. Conclusion

In conclusion, physical exercise improves non-alcoholic fat liver disease (NAFLD), however an optimum approach is still unclear. Regardless, a regular and long-term systematic practice of exercise leads to a better general health, body weight control, and life quality improvement. Interestingly, findings of the reviewed authors are quite varied and of the low significance level. However, 90% of them have shown a positive and/or beneficial impact on the subjects, without necessarily reducing the fat content specifically of the liver though. Therefore, NAFLD and NASH require pharmacological intervention, and physical exercise is an adjunctive therapy to enhance the effect of medication. Further studies should be carried out in humans under drug therapy to assess the impact of exercise on the effect of drugs. Furthermore, more specific studies involving animals are needed in order to reach accurate guidelines for future human applications, considering that although studies based on anthropometric and histochemical measurements have not shown significant impact on the measured parameters, most of them have, indeed, shown, in practice, to varied extents, improvements in several aspects analyzed, molecular research, both in animals and in humans, should be done seeking for more visible and measurable beneficial changes.

### List of Abbreviations

NAFLD: Non-alcoholic fat liver disease; MRI: Image Resonance Magnetic; ALT: Alanine transaminase; AST: Aspartate transaminase; TG: Triglycerides; NASH: Non-alcoholic steatohepatitis; HCC: Hepatic cellular carcinoma; FDA: Food and Drug Administration; EX: exercise; CR: Caloric restriction; AMPK: AMP-activated protein kinase; FGF21: Fibroblast growth factor 21; VLDL: very-low-density lipoprotein; HR: heart rate; H. R Max: Heart rate maximum; mTORC1: mammalian target of rapamycin; TNF-α: Factor de Necrose Tumoral Alfa; IL-6: interleucina 6; AIT: aerobic interval training; HTGC: hepatic triglyceride content; IHCL: intrahepatocellular lipids.
Available of Data and Material

All available data’s and material are found in the manuscript.

Competing Interests

The authors declare that they have no competing interests.

Contributions

MFLF and FPS: Conceived the design, searching the literature, drafting the manuscript; FPS, IPC, MAF and WFB: searching literature, supervising and critical review of the manuscript. All authors read and approved the final manuscript for publication.

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