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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

hyperinsulinemia, adipose inflammation, and hypoadiponectinemia deregulate the turnover of one or more hepatic lipid reservoirs, leading to lipid accumulation in the hepatocytes that leads to inflammation, a process known as lipotoxicity [40, 48].

Regardless of having no FDA (Food and Drug Administration)-approved pharmacologic therapy is currently available, lifestyle changes have been suggested as a nonpharmacologic option to combat NAFLD associated with metabolic conditions. The guidelines for NAFLD treatment recommend the combination of daily exercise and caloric restriction, targeting at 3–10% weight loss [5].

The compilation, such as metabolic disorders, contribute to cardiovascular and cerebrovascular events, the major causes of death in NAFLD. However, these findings justify the importance of targeting the skeletal muscle in NAFLD to induce lifestyle modifications that improve cardiovascular and cerebrovascular morbidity and mortality. Studies on physical exercise in NAFLD shows significant benefits on hepatic steatosis, serum transaminases, lipid profile, and glycemic control that can potentially lower cardiovascular and cerebrovascular events [22].

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].

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 Wang, B. et al. [28], 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 stablish 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], Shojaee-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 60 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
	N	Intensity	Session length	Session frequency	Time of intervention	Results that there was improvement						
KAWANISHI, N. et al., [11]	34/4	15 – 20 m/min	60 min	5 x week	16 weeks	% Fat	ALT	TNF-α, IL-6	TG	–		Significantly
AAMANNA, L, et al. [23]	26/2			5 x week	4 weeks	% Fat	ALT	AST	_	_		Moderate
BATATINHA, H. A. P. et al., [9]		60% VO_2 Max.	60 min	5 x week	12 weeks	% Fat	Weight	Glucose	ALT	TNF-α IL-6		Significantly
CHO, J. et al., [2]		12 m/min	50 min	5 x week	16 weeks	% Fat	Weigh	ALT	TG	TNF-α IL-6		Beneficial
GONÇALVES, I. O. PASSOS, E. DIOGO, C. et al. [26]		15-25 m/min	60 min	5 x week	17 weeks	Mitochondrial Improvement						Beneficial
MIOTTO, P. M. et al. [29]	16/8	15 m/min	45 min	5 x week	4 weeks	% Fat	Weigh	TG				Beneficial
ROSA-CALDWELL, M. et al. [13]	20/2	Voluntary roads			4 weeks	AST	TNF-α IL-6	–	–	–		Significantly
WANG, B. Et al. [8]		10 m/min	60 min	4 x week	24 weeks	ALT	TG	TNF-α IL-6	Stress oxidative			Beneficial
WINN, N. C. et al. [33]		Voluntary roads			10 weeks	Weigh	Glucose					Beneficial
XIAO, J. et al. [1]	40/4	10 m/min	60 min	5x week	16 weeks	Weigh	Insulin	AST	Alt	TG	Stress Oxidative	Beneficial
YOSHIMURA, S. et al. [35]		Voluntary roads			6 weeks	% Fat	ALT					Beneficial
KAPRAVELOU, G. et al, [7]	80/10	65-80% V VO_2 Max. HIT	60 min	5x week	8 weeks	% Fat	AST	ALT	Glucose	TG		Beneficial
MOON, H. Y. et al. [12]	19/2	10 m/min	50 min	5 x week	4 weeks	%Fat	ALT	TG				Significantly
HACZEYNI, F. et al. [48]		Voluntary roads			4 weeks	Weigh	ALT	Insulin				Beneficial
FRANTZ, E. D. C. et al. [38]	32/4	50-75% VO_2 Max.	60	4 x week	8 weeks	TNF-α IL-6						Beneficial
LINDEN, M. A. et al. [47]	30/10	15/20m/min 40 m/min	60 min 30 min	5 x week	12 weeks	%Fat	Weigh	Insulin	Glucose	ALT	TNF-α IL-6	Beneficial

Author	Method					Results					Conclusion
	N	Intensity	Session length	Session frequency	Time of intervention	Results that there was improvement					
MARCINKO, K. et al. [14]		15-22 m/min	sprint 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
GONÇALVES, I. O. et al. [10]		15-25 m/min	60 min	5 x week	8 weeks	%Fat	Stress Oxidative				Beneficial

N = number of participants, VO_2 oxygen volume

The human studies have yielded 3 types of results as shown 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 60 to 75% HR max, 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, Takahashi A, eta 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] have 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					Results							Conclusion
	N	Intensity	Session length in times	Session frequency	Time of intervention	Results that there was improvement							
KULLMAN, E. L. et al. [46]	22	85% HR Max.	60 min	7days	7days	Glucose	Insulin						Beneficial
OH, S. et al. [16]	72	40% HR Max,	90 min	3x week	3 moths	Diet had more benefits							No Influence
SHOJAEE, F. et al. [22]	29	40-60% HR Max.	60 min	4x week	16 weeks	%Fat	AST	ALT	Weigh	IMC	Circumference	Insulin fasting	Beneficial
TAKAHASHI, A. et al. [6]	53	3x10 rep	30 min	3x week	12 weeks	Weigh	IMC	ALT	AST	Insulin	Cholesterol	IHCL	Beneficial
TUTINO, V. et al. [32]	142	60-70% HR Max.	45 min	3x week Body building		IMC	HDL	HOMA-IR					Beneficial
YOSHIMURA, E. et al [34]	89		60 min	3x week	12 weeks	%Fat	TG	TNF-α IL-6	IMC	Visceral fat index			No Influence
ZELBER-SAGI, S. et al. [15]	64	60-75%	45 min	3X Week Body building	3 moths	Weigh	IMC	Cholesterol Total					Significantly
HOUGHTON, D. et al. [21]	24	Hard	45-60% HR Max.	3x week	12 weeks	%Fat	TG	Insulin	HTGC				Beneficial
ZANG, H-J. et al. [36]	208	45-55% 65-80% HR Max	30 min	5x week	12 mouths	Weigh	TG	Circumference	Risk Factors				Beneficial
TANIGUCHI, H. et al. [20]	27	60-75%	45 min	3-5x week	5 weeks	%Fat	AST	TG	%Fat visceral				Beneficial
CROCI, I. et al. [17]	16	50% 1RM	60 min	3x week	6 moths	%Fat	Diet had more benefits						No Influence
PUGH, C. A. J. et al. [45]	21	45-60% HR Max.	45 min	3-5x week	16 weeks	IMC	Weigh	Glucose	Circumference				Beneficial
MACLEAN, C. et al. [18]	9	Sprint 5 shots	60 min	2x week	6 weeks	%Fat							No Influence
AL-JIFFRI, O. et al. [5]	100	65-75% HR Max.	40 min	3x week	3 moths	IMC	ALT	AST	Insulin				Significantly

Author	Method					Results	Conclusion
	N	Intensity	Session length in times	Session frequency	Time of intervention	Results that there was improvement	
MALIN, S. K. et al. [19]	13	85% HR Max.	60 min	7 Days	7 days	Fetuin-A	No influence

HR = heart rate; Fetuin-A = are blood proteins that are produced in the liver and secreted into the bloodstream

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 authhor 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 FGF21without 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.

Availability 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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