

Effects of Aerobic Physical Training in Non-Alcoholic Fat Hepatic Disease Aspects Related to Mitochondrial Biogenesis and Oxidative Stress: A Review

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is one of the most com-

mon forms of liver disease, affecting about 20% to 30% of the adult population, being found more often in obese individuals (~ 90%). Among the main etiological factors are insulin resistance, mitochondrial dysfunction and oxidative stress. To date, no specific pharmacological treatment for NAFLD, so lifestyle modifications such as: reduction in body weight, diet and regular practice of aerobic physical exercise are effective, however it is not yet elucidated what the main impacts of physical exercise on NAFLD.

Key words: Aerobic exercise; Mitochondria and Hepatic Steatosis

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most frequent forms of liver disease and is related to the obesity and physical inactivity around the world. This disease encompasses a spectrum of liver changes ranging from the simple deposition of intrahepatic fat, without inflammation or fibrosis, to more severe cases such as non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC)^[1,2]. NAFLD is increasingly in all populations, especially the western society. In addition, the industrialization process, imbalance in the intake of macronutrients and sedentary lifestyle, contribute to the development of this pathology^[3].

The installation of NAFLD has high complexity and a variety of etiological factors, among which the following stand out obesity, insulin resistance (IR) and cardiorespiratory diseases^[4]. Insulin resistance is the result of excessive consumption of carbohydrates (CHO),

providing translocation of glucose transporters to the cell membrane, with a consequent increase in the influx of glucose into the cell, reducing the functionality of insulin receptors (IRS-1 and IRS-2) and increasing lipogenesis^[4-6]. The emergence of new technologies has provided human beings with important benefits in their daily lives, however, similarly, it can provide low levels of physical activity, making people increasingly sedentary^[7].

This discussion is extremely important, since sedentary lifestyle, associated with inadequate nutrition, contributes to the emergence of chronic non-transmissible degenerative diseases (NCDs) and an increase in the mortality rate between men and women^[8]. Aerobic exercise is characterized by having low-intensity standards 40-50% of the maximum oxygen volume (VO₂ Max), preceded by a longer duration of the activity using lipid oxidation with the substrate for energy supply, during exercise physical. In addition, benefits are found in mitochondrial biogenesis, caused by the increase in the number of mitochondria, functionality, and reducing damage caused by the excessive production of EROS^[9,10].

Thyfault et al^[11] in an experimental model with rats, demonstrated that having low mitochondrial oxidative capacity guarantees susceptibility to NAFLD, by providing, among other things, a greater lipogenic phenotype in the body. Rector and collaborators demonstrated that regulating the practice of aerobic physical activity at an intensity of 85% of the maximum oxygen volume for 12 weeks was able to reduce levels of intrahepatic triglycerides and improve sensitivity and resistance to insulin, without providing significant weight loss. However, when physical activity provides weight loss at significant levels, the benefits are doubly enhanced^[12-14].

However, the study emphasizes limitations linked to adherence to the practice of regular exercise in studies with human beings. When analyzing the relationship between patients with NASH and mitochondrial functionality, Carreras and collaborators analyzed the activity of five complexes of the electron transport chain^[15]. In their results, it was found that these patients, when compared to the control group, had a reduction in activity five in the mitochondrial complexes, resulting in an energy deficit, inflammatory response, and lipogenesis^[16,17]. According to the relevance and impact of non-alcoholic fatty liver disease, on epidemiological, clinical and pathophysiological parameters and considering its potential for chronification to more severe pathological stages such as liver cirrhosis and HCC, the objective of this mini review was to evaluate the various effects of aerobic physical exercise in mitochondrial biogenesis and oxidative stress under NAFLD conditions^[18].

SEDENTARY LIFESTYLE AND NAFLD

The emergence of new technologies has provided human beings with important benefits in their daily lives, however, similarly, it can provide low levels of physical activity, making people increasingly sedentary^[19]. This discussion is extremely important, since sedentary lifestyle, associated with inadequate nutrition, contributes to the emergence of chronic degenerative diseases (CDs) and an increase in the mortality rate between men and women^[20]. Bae et al. conducted a study with 72,359 non-obese Korean individuals, using an international physical activity questionnaire (IPAQ). The results demonstrated an association between high levels of physical activity and reduced risk of obtaining NAFLD, improved lipid profile and reduced values of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These findings indicate that physically active patients have better liver and biochemical conditions. In addition, changes in the sedentary lifestyle prevent the installation of NAFLD

and associated comorbidities^[21].

It is conceptually defined by adaptations in the cardiorespiratory system mediated by aerobic predominance stimuli, among which physical exercise stands out as one of the main ones. The results showed that individuals who had a low aerobic capacity, were more susceptible to NAFLD. This mechanism can be understood, since changes in oxidative metabolism can generate mitochondrial dysfunctions, causing energy deficit and consequent increase in the storage of fats in the liver^[22]. In other hand, benefits are found through aerobic exercise on mitochondrial biogenesis, caused by the increase in the number of mitochondria, functionality, and reducing damage caused by the excessive production of EROS^[23]. Thyfault et al. in an experimental model with rats, demonstrated that having low mitochondrial oxidative capacity guarantees susceptibility to NAFLD, by providing, among other things, a greater lipogenic phenotype in the body^[11].

Linden et al., demonstrated that regulating the practice of aerobic physical activity at an intensity of 85% of the maximum oxygen volume for 12 weeks was able to reduce levels of intrahepatic triglycerides and improve sensitivity and resistance insulin, without providing significant weight loss. However, when physical activity provides weight loss at significant levels, the benefits are doubly enhanced. However, the study emphasizes limitations linked to adherence to the practice of regular exercise in studies with human beings^[24].

When analyzing the relationship between patients with NASH and mitochondrial functionality, Carreras and collaborators analyzed the activity of the five complexes of the electron transport chain. In their results, it was found that these patients, when compared to the control group, had a reduction in activity five in the mitochondrial complexes, resulting in an energy deficit, inflammatory response, and lipogenesis^[25].

In contrast, Gonçalves and collaborators demonstrated that physical activity can prevent mitochondrial dysfunctions, through modulation in oxidative and bioenergetics metabolism. This mechanism consists of an increase in the intramuscular and hepatic activity of adenosine monophosphate kinase (AMPK), which inhibits factors associated with lipogenesis, among which the following stand out: Sterol transport regulator (SREBP1C) and fatty acid synthesis (FAS), leading to decreased inflammatory response, oxidative stress and mitochondrial damage. However, it is not clear how physical exercise modulates mitochondrial biogenesis and energy decrease^[26,27].

NAFLD, Oxidative Stress and Aerobic Exercise

Within the characteristic pathophysiology found in non-alcoholic fatty liver disease, oxidative stress (OE) stands out as one of the factors that contribute to the progression of the clinical staging of its patients. EO is characterized by the overproduction of EROS, associated with the imbalance and decreased levels of antioxidant enzymes responsible for removing these compounds from the cellular environment^[28]. Among the substances that are produced, hydrogen peroxide (H₂O₂) stands out, this substance in the intracellular environment causes macrophage activation, which in turn expresses pro-inflammatory cytokine, in addition, the metabolic imbalance provides functional overload in the mitochondria, which in the long run term causes mitophagy, mitochondria degradation process and subsequent autolysis of this organelle^[28-30].

Antioxidant defenses are responsible for the regulation and elimination of EROS in body tissues, in a state of body homeostasis there is a balance between these two physiological components. These active compounds are found in two forms: antioxidant prevention enzymes, which act in a prophylactic manner, preventing imbalances

from occurring within the redox processes, among which are: Catalase and Glutathione peroxidase; and another enzymatic type, chain cleavage antioxidants, which act during the execution of the EO production process, trying to bring the redox processes back to normal^[9].

Bringing the DHGNA pathophysiology scenario, the lipid peroxidation process appears as a determining factor for the production of EROS, since the liver stops oxidizing lipids (physiological exothermic reactions mediated by molecular oxygen, whose final product is the production of water (H₂O) and carbon dioxide (CO₂) and starts to peroxide lipids (reactions mediated by the consumption of molecular oxygen)^[31,32]. This excessive production of superoxide and peroxide anions cause cellular and molecular damage since when once these peroxides are activated, they stimulate the production of pro-inflammatory cytokines, lipotoxicity, metabolic disorders and reduced functional capacity of mitochondria and damage to their deoxyribonucleic acid (DNAmt), these factors contribute to the progression of NAFLD^[33,34].

Regarding hepatic fibrogenesis, EROS also plays a fundamental role in the activation and synthesis of hepatic stellate cells, cellular elements which, in a physiological state, are quiescent within hepatocytes^[35,36]. Since there is an increase in the production and cellular signaling of inflammatory factors synthesized by intrahepatic lipogenesis and EROS as a tumor necrosis factor-alpha (TNF- α), nuclear factor Kappa B (NFKB), Kupper cells and neutrophil infiltration, these stellate cells start to express proteins linked to the extracellular matrix of hepatocytes and start the production of collagen causing varying degrees of fibrosis^[2,37,38].

On the other hand, physical exercise appears as a regulating factor in this process, since it is responsible for the increase in the production of antioxidant enzymes and has a positive response in inflammation, increasing the production of anti-inflammatory cytokines at moderate intensity^[8]. Souza et al^[39] in a review study demonstrated that the regular practice of non-strenuous aerobic physical exercises (those that do not provide an excessive degree of muscle fatigue), is able to regulate the oxidative stress, increase muscle activation and provide greater mitochondrial biogenesis. This mini-review demonstrates that there is a need to establish a target zone in relation to the intensity, frequency, and duration of physical exercise for patients with NAFLD, in order to maximize results and avoid possible negative developments in the clinical staging of these individuals, in addition to improving adherence to physical exercise programs and lifestyle changes^[40,41].

NAFLD, Mitochondria, and Aerobic Exercise

Within the range of organelles existing in our cells, the mitochondria stand out for having multiple functionalities, among which we can mention: energy production, metabolic activity, intracellular respiration essential for maintaining cellular homeostasis. In addition, it has its own genetic material (DNAmt) responsible for gene transcription and translation of specific proteins^[42,43]. The mitochondria have a rounded or elongated morphology, with two lipoprotein membranes: internal and external, responsible for the transport of enzymes, ions, and substrates such as CO₂, these specialized transport proteins that are called: translocases. In addition, between these membranes, there is a space called intermembrane with metabolically active enzymes that stimulate processes linked to cellular metabolism^[43,44].

However, what makes mitochondria an indispensable and fundamental cellular component is its ability to produce adenosine triphosphate (ATP), this energy "currency" is responsible for the supply of energy to our organism and can be obtained by three reducing oxide reactions, which are: (1) glycolysis, which consists of the catalysis

of glucose into pyruvic acid, which in turn gives rise to pyruvate. It reacts with acetyl-coenzyme a (acetyl-CoA), and enters the internal mitochondrial membrane by translocation, initiating the (2) Krebs cycle or tricarboxylic acids. The energy and electronic balance of the cycle are sent to the (3) electron transport chain (CTE), which has five multi-enzyme complexes responsible for electron capture and conversion into a balance of 36-38 ATP's^[42].

In skeletal muscle, mitochondria are linked to the specialization of type one muscle fibers (slow-twitch fibers), which predominantly use the oxidative metabolic pathway. Once the state of skeletal muscle inactivity or muscle disuse is established, the mitochondrial content (morph mitochondrial functionality) is modified, so that transcription levels of the alpha peroxisomal proliferation co-activator (PGC-1 α) significantly reduce^[39]. This, in turn, is the main indicator of the mitochondrial biogenesis process that is characterized by the production of new mitochondria and that, concomitantly, provides significant increases in molecular oxygen levels and aerobic fitness^[45,46].

PGC-1 α is linked to the muscle activation pathway through its interaction in the ATP / adenosine monophosphate (AMP) rate, which in turn is related to the expression of adenosine monophosphate kinase (AMPK). This protein, when activated by muscle contraction by aerobic routes, performs the phosphorylation and transcription of PGC-1 α , it interacts with respiratory nuclear factors 1 and 2 (NRF-1 and NRF-2), for the transport of DNA and stimulation of biogenesis mitochondrial^[47]. When the body is stimulated by aerobic physical exercise, it produces different organic responses, among them, the increase in aerobic capacity or aerobic fitness, which is conceptually related to a higher level of molecular oxygen captured and the performance of activity with the lowest energy expenditure, which characterizes metabolic efficiency^[48,49].

Ferreira and collaborators^[50] carried out a protocol for assessing the maximum lactate level produced in the blood, stable lactate and lactate levels in the face of an effort load (workload) of 60% of the animals' running speed, for this, 32 C57BL / 6J mice were used, which were divided into two groups (trained n = 15 and sedentary n = 17). The results found showed that the group that practiced physical training, produced a higher level of produced speed, in addition to higher levels of lactate in response to effort, associated with these results there was a bradycardia response in these animals in 21% in relation to the sedentary group. This demonstrates that aerobic exercise was able to produce significant adaptations in the cardiovascular system^[31,51].

This study was fundamental, as it served as standardization of this protocol for mice of this lineage, proving to be reproductive, after blind analysis among researchers. Another study with aerobic exercise by Rector and collaborators made a comparison between groups of C57BL / 6J mice, which were divided by the level of respiratory capacity into high respiratory capacity (high capacity respiratory - HCR) and low respiratory capacity (Low capacity respiratory - LCR). The results showed that the HCR group had a lower level of intrahepatic triglycerides, preceded by higher levels of cytochrome c, citrate synthase and intrahepatic b-hydroxyethyl-co-A dehydrogenase (β -had)^[8,19,52].

This demonstrates that mice that practiced aerobic physical exercise had better mitochondrial functionality, reflecting an improvement in NAFLD levels, confirmed by histological analysis and lower levels of SREBP1C found in the HCR group. Another important result was found in the assessment of the area of fibrogenesis and nuclear apoptosis of intergroup hepatocytes, the HCR group had a smaller fibrous area and a lower level of nuclear hepatocyte apoptosis^[53-56].

Therefore, it is evident that mice with NAFLD, who had a low

level of cardiorespiratory fitness, are more susceptible to severe energy disorders capable of providing a higher rate of clinical and pathophysiological evolution. On the other hand, the regular practice of aerobic physical exercise is able to provide stimuli and adaptations in the cardiorespiratory system, being able to produce a higher level of molecular oxygen by mitochondrial biogenesis. However, the mechanisms that generate such benefits are still largely unknown.

CONCLUSION

Aerobic physical exercise had positive effects on the stimulation of mitochondrial bioenergetics and on the reduction of oxidative stress, resulting in an improvement in the condition of non-alcoholic fatty liver disease.

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