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Mini Review

NAFLD as a Silent Disease and the Risk of Cardiovascular Mortality: The Role of Diet and Physical Exercises

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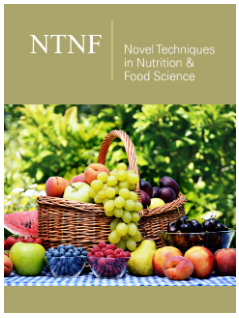

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is closely linked to behavioral factors (sedentary lifestyle and dietary inadequacy). It is the most frequent liver disease in the world (25%), in which the deposit of hepatic fat culminates in pathological outcomes, impairing hepatic metabolism and increasing the risk of Cardiovascular Diseases (CVDs). In contrast to usual conduct with the use of drugs for the treatment of NAFLD, lifestyle modification programs are presented as a potential non-pharmacological strategy in the modulation of NAFLD. In a healthy and low-cost way, the practice of physical activity, physical exercises, and adequacy of diet are excellent alternatives for the prevention and treatment of NAFLD and reduction of CVDs risk factors.

Keywords: Non-alcoholic fatty liver disease; Cardiovascular risk; Non-communicable diseases; Diet; Physical activity; Physical exercises; Lifestyle modification program

Introduction

Human evolution and non-communicable diseases

Non-Communicable Diseases (NCDs) in the contemporary world have as their main causal factor human behavior based on epidemiological-demographic and dietary transitions [1]. Paleolithic man (hominids) was essentially "hunter-gatherer-nomad", adopted hunting, fishing, and gathering fruits and roots for food subsistence, did not have a fixed home and showed high energy expenditure in physical activity, due to constantly moving (approximately 10 miles per day) looking for food, looking for housing and escaping predators [1]. Thus, they had a good quality diet, rich in protein and fiber, combined with high energy expenditure, providing evolutionary monitoring and survival conditions [2]. On the other hand, we have the Industrial Revolution as a significant milestone in this process of epidemiological and food transition, where man began to enjoy greater ease in obtaining food, but they gradually lost their natural properties to the detriment of refinements and industrial processes, making them those with lower nutritional quality, associated with increasingly less physically active work activities, due to the insertion of machinery and automation [2]. Consequently, the lifestyle has been establishing itself with increasingly sedentary habits and increasingly high energy intake (positive balance) and diet of poor quality, contributing to the development of NCDs, among them, emphasis on Non-Alcoholic Fatty Liver Disease (NAFLD) [3].

Non-alcoholic fatty liver disease

NAFLD is a silent, multisystemic disease closely linked to behavioral habits (sedentary lifestyle and poor eating habits), culminating in pathological outcomes, including Cardiovascular Diseases (CVDs) [4]. NAFLD is the most common liver disease in the western population, defined as >5% hepatic steatosis or a chronic condition of fat accumulation in the liver (identified by imaging or liver biopsy) in the absence of chronic or excessive consumption of alcohol, medications inducers of steatosis and other liver diseases, hereditary diseases and/or viral infections [5]. Histologically, NAFLD includes non-alcoholic fatty liver disease, with fatty liver without evidence of hepatocyte damage, and Non-Alcoholic Steatohepatitis (NASH), the latter with fatty liver and lobular inflammation associated with hepatocyte damage with or without fibrosis [5]. The average prevalence of NAFLD is approximately 25% in the adult

world population [6]. Clinically, patients with NAFLD tend to be obese and may have insulin resistance or type 2 Diabetes Mellitus, dyslipidemia, and hypertension, which are risk factors for CVDs [7]. In the progression of NAFLD, non-alcoholic hepatic steatosis, 10-30% can evolve to NASH, and 25-40% of individuals with NASH can evolve to progressive hepatic fibrosis, culminating in cirrhosis (20-30%), with high risk of complications and progression to the final stage, one of the main complications observed is hepatocellular carcinoma (16%) [5,8]. Still, CVDs are the leading cause of mortality in NAFLD (approximately 40%) [9].

NAFLD occurs due to an imbalance between the influx of Free Fatty Acids (FFAs) from peripheral lipolysis (adipose tissue) and their use (beta-oxidation) or mobilization for circulation (very low-density lipoproteins) [10]. This excess of intrahepatic FFAs is compounded by de novo lipogenesis from excess dietary carbohydrates and fats [11]. Because of this bioenergetic incompatibility, there is an accumulation of triglycerides and FFAs metabolites, which have pro-inflammatory, pro-oxidative and pro-apoptotic properties, contributing to cellular lipotoxicity, worsening of systemic and local inflammation and hepatic insulin resistance [10]. NAFLD exhibits a proatherogenic serum lipid pattern composed of low HDL cholesterol and high triglyceride levels, small and dense LDL particles, and high levels of apolipoprotein B100. Lipoproteins containing apolipoprotein B, after penetrating and undergoing oxidation in the subendothelial vascular wall, there is induction of inflammation of the vascular endothelium and atherosclerosis [12]. Insulin resistance corroborates beta cell dysfunction, activates transcription factors involved in de novo lipogenesis and vascular inflammation, atherogenesis processes, progression of atherosclerotic lesions and platelet vulnerability [13]. Compromised angiogenesis is another contributing factor to platelet instability and vulnerability [12]. As well as the imbalance of pro-and anticoagulants, they result in a greater production of pro-thrombotic factors, hypercoagulability, and impairment in the supply of nutrients and oxygen to the tissues [13]. Considering the severity of NAFLD and its potential CVDs risk, it is necessary to adhere to non-pharmacological therapeutic strategies in the medium and long term to maintain the health of these patients and NAFLD regression in a healthy and low-cost.

Non-Pharmacological Therapeutic Strategies for NAFLD

The main primary approach for the prevention and treatment of NAFLD is the lifestyle change. This change includes dietary adequacy and physical exercises, which favor weight loss, improvement of biomarkers related to hepatic metabolism and other conditions (oxidative-inflammatory stress, resistance insulin and hypertension), in addition to the reduction of liver fat and cardiovascular risk [14-17]. Physical activity and exercise are excellent low-cost alternatives for NAFLD treatment. Studies show many benefits with physical exercise contemplating weight loss, reduction of liver fat and improvement of other related biomarkers [14-17]. In general, moderate-intensity physical exercise and practiced at least 4x a week was the most effective in NAFLD regression [14-17]. Specifically, studies show that aerobic exercise has more beneficial effects compared to resistance and combined exercise (aerobic+resistance) [14,16,17]. The exercise has shown improvement of biomarkers related to hepatic metabolism and reduction of intrahepatic fat content, regardless of body weight loss. The improvement in muscle mass brought benefits in insulin sensitivity, enhances activity of key enzymes involved in β-oxidation, increases sensitivity of adipose tissue to epinephrine-stimulated lipolysis, increases oxidation of intra-muscular triglycerides, reduces liver fat, and reduces liver damage [10]. Additionally, exercise is associated with enlargement and increase of mitochondria in skeletal muscle. Mitochondria play an important role in hepatocyte metabolism, representing the primary site for fatty acid oxidation and oxidative phosphorylation [10].

Diet is another key point in NAFLD regression. Diet modifications involve both total energy intake and diet composition. First, high caloric intake favors excess energy with a pattern of lipid deposits not only in adipose tissue, but also in liver tissue [18]. High carbohydrate intake and refined carbohydrate intake are a major stimulus for hepatic de novo lipogenesis, in addition to contributing more directly than dietary fats to NAFLD [18]. After all, the substrates most used in the synthesis of fatty acids newly produced by hepatic de novo lipogenesis are mainly glucose, fructose, and amino acids [18,19]. Also, foods high in saturated fat, such as high-fat dairy products and processed meats, favor the progression of NAFLD [18,19]. The consumption of unsaturated fatty acids and dietary fiber increases satiety, improves insulin sensitivity, reduces de novo lipogenesis, and modulates the intestinal microbiota, contributing to the regression of NAFLD [19]. The Mediterranean diet has shown positive effects on NAFLD and CVDs risk due to the intake of oils such as unsaturated fatty acids, including polyunsaturated and monounsaturated fatty acids whose main sources are fish, nuts, seeds, and vegetable oils [19,20]. In addition, the Mediterranean diet features a good intake of fruits, vegetables, and legumes. Its effects can be conferred by the better quality of ingested fat and food sources rich in fiber and phenolic compounds [20]. Another additional effect of the diet is the modulation of hepatic lipotropic nutrients. Choline is a vital component of cell membranes as a constituent of phosphatidylcholine formed in the methionine transmethylation pathway [21]. It is essential for liver lipid metabolism. Therefore, the output of VLDL from the liver is dependent on nutrients considered lipotropic agents, such as methionine, betaine, riboflavin, pyridoxine, choline, folate, and cobalamin [21]. Additionally, the maintenance of the intestinal microbiota, important in the metabolization of several nutrients, including choline, protects the liver against the NAFLD progression [21]. There are few Lifestyle Modification Programs (LSMP) with the practice of physical exercises combined with dietary intervention in NAFLD, yet studies have shown improvements in NAFLD due to the synergistic effect, dietary adequacy plus physical exercises [22,23]. LSMP already demonstrate prevention of NAFLD. Besides, patients with NAFLD undergoing LSMP demonstrated greater weight loss, greater insulin sensitivity, improvement in biomarkers related to hepatic metabolism and greater reduction in hepatic fat content, in

addition to greater reduction in CVDs risk factors, when compared to isolated interventions of physical exercises or diet [14,15,22,23].

Conclusion

NAFLD is a silent disease and its emergence and aggravation to cardiovascular complications is closely related to lifestyle factors, such as sedentary lifestyle and dietary inadequacy. The need for non-pharmacological therapeutic strategies, such as changes in lifestyle, has become essential in the prevention and treatment of NAFLD. Public policy with the creation of LSMP can be highly effective across the course of NAFLD and CVDs risk. Additional investigations are essential to elucidate the best strategies to avoid the use of pharmacological treatment, thus having lifestyle changes as the focus in patients with NAFLD.

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