Review Article

The relationship between NAFLD with diet and exercise: Current perspectives

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Abstract

NAFLD, a general term that describes several diseases caused by hepatic fat deposition such as hepatic steatosis (HS) and nonalcoholic steatohepatitis (NASH), includes the many conditions that are related to fat accumulation in the liver. Indeed, NAFLD is treated with a treatment plan consisting of weight loss, nutritional supplementation, and physical activity. Despite the lack of scientific research on diet and physical exercise, there is a paucity of evidence on NAFLD. The DASH and Mediterranean diets have been frequently used for treating cardiovascular metabolic risk factors, such as insulin resistance and type 2 diabetes mellitus (T2DM). In this study, an in-depth assessment of existing dietary and physical activity methods, involving Brazilian and other country-specific recommendations was conducted to determine their effect on the risk of nonalcoholic fatty liver disease (NAFLD).

Key Words: **Hepatic steatosis, NAFLD, Diet, Exercise training**

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a broad term that refers to a group of liver disorders mostly caused by fat buildup in the liver. These conditions are collectively referred to as hepatic steatosis. However, in addition to hepatic steatosis, there must be inflammation, ballooning, and moderate fibrosis for NASH (nonalcoholic steatohepatitis) to evolve into cirrhosis and HCC (liver cancer) (Figure 1).

There are some differences between alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) but one major difference is that NAFLD occurs in individuals that drink much less 20–40g of alcohol g/day (Farrell & Larter, 2006). Nonalcoholic fatty liver disease (NAFLD) is already one of the main common causes of liver disease, comprising between 20% to 30% of the patients in industrialized nations. Its incidence has increased significantly in recent years due to the Western world's obesity epidemic, which is mainly caused by a sedentary lifestyle and bad eating habits (Masarone et al., 2014).

One-quarter of the US community is considered obese, with 80% of these individuals afflicted with NAFLD (or nonalcoholic fatty liver disease) (Brunt et al., 1999). It affects 90% of those with class III obesity [BMI > 40 kg/m^2]. The occurrence of NASH varies between 2% and 3% (Bellentani et al., 2010). NAFLD is prevalent in individuals with diabetes mellitus, and increasing data suggests that diabetic patients (T2DM) are at a greater risk for progressive types of NAFLD, NASH, severe liver fibrosis, hepatocellular carcinoma, and liver-related mortality (Leite et al., 2014). The NAFLD incidence ranges from 42.6 to 79 percent in these individuals (Williamson et al., 2011). It should be mentioned that these figures differ from nation to nation and almost 13% of the people already show signs of cirrhosis (Dvorak et al., 2015). In the US community with type 2 diabetes and normal serum aminotransferase values, NAFLD and NASH were seen to be common (Portillo-Sanchez et al., 2015).

Obesity, genetics and insulin resistance all contribute to hepatic

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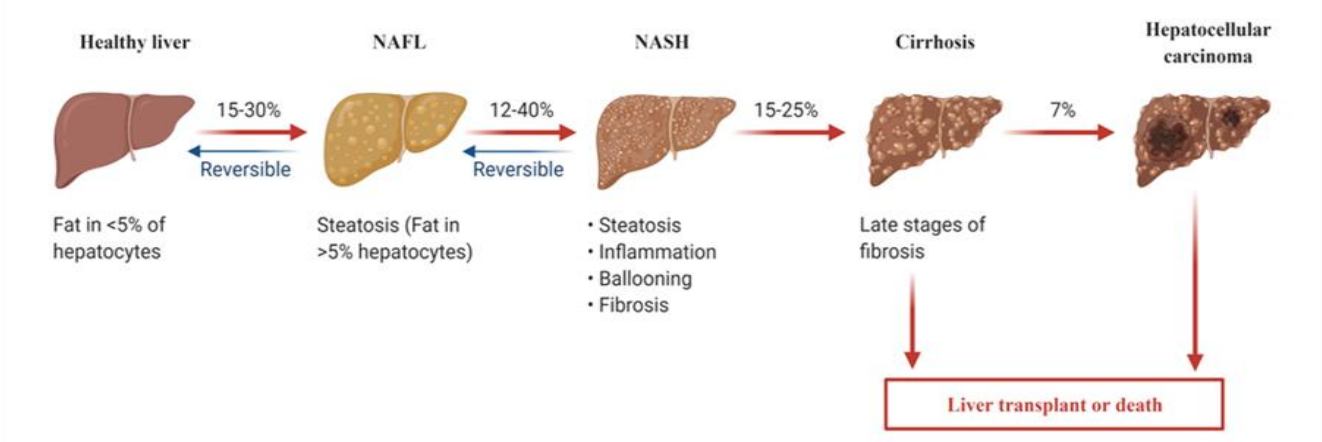

Figure 1. Nonalcoholic fatty liver disease (NAFLD) spectrum.

fat accumulation. NASH affects 12-40 percent of individuals with NAFLD and may develop to cirrhosis in 15-25 percent of cases within 20 years. Additionally, 7% of cirrhosis patients develop HCC. Thus, the goal of this review was to examine the function of food and physical exercise as an alternative to pharmacological treatment for NAFLD.

Caloric imbalance

Obesity has become an epidemic in the past half-century. On the other hand, 650 million individuals (13 percent of the adult population) were obese in 2016, with a BMI of 30.0 kg/m2 (Marchesini et al., 2016; McCarthy & Rinella, 2012). NAFLD, affecting 24% of the worldwide population, is currently the primary cause of liver disease. Both diabetes and cardiovascular disease are powerful moderators of nonalcoholic fatty liver disease (NAFLD). The rate of nonalcoholic fatty liver disease almost triples in people with diabetes, and cardiovascular disease (McKay et al., 2018; Shaikh et al., 2019). Although obesity affects children and adolescents, it is also a threat to them. Hepatic steatosis affects 28 percent (1.5 million) of obese children and adolescents in the European Union, with 4.6 percent having metabolic syndrome and a higher risk of heart disease progression (Cleveland et al., 2018).

From 1993 to 2003, 9.6% of individuals aged 2 to 19 years and 38% of obese children autopsied in the United States had evidence of hepatic steatosis (Dai et al., 2017). The UK's Scientific Advisory Committee on Nutrition claims that people have a diet that is 50% carbohydrate (CHO) and less than 35% fat, with 0.75 g protein per kilogram of body weight (Allen et al., 2018). In a study, the average daily macronutrient intake was measured by UK Biobank database. More than half of the participants in the survey showed in the meal memory tests it exceeded their recommended daily calorie intake, even though the participants as a whole consumed below the necessary daily energy intake, according to the data from the study (Jackson-Leach & Lobstein, 2006).

Energy limitation function

Obesity and its comorbidities are a major risk factor for NAFLD (Georgoulis et al., 2015). Additionally, independent of baseline body mass index, weight increase of any magnitude, even 3–5 kg, predicts the development of NAFLD (BMI) (Albano et al., 2005). Snacking, a common feature of the Western diet, increases both liver fat (as revealed by MRS) and belly fat (as assessed by MRI), indicating that snacking is an independent contributor to hepatic steatosis (Oliveira et al., 2002).

The importance of dietary ingredients

Omega-3 polyunsaturated fatty acids (PUFAs)-rich regimens have been found to increase insulin sensitivity, decrease intrahepatic triglyceride levels, and ameliorate steatohepatitis. According to clinical data, patients with NAFLD and NASH eat less omega-3 polyunsaturated fatty acids (PUFAs) and have a higher n-6/n-3 ratio than normal group (Abdul-Hai et al., 2015; Zamara et al., 2004). Furthermore, increased PUFA and SFA intake has different impacts on the development of liver and visceral fat in adults. Likewise, a ten-week randomized controlled trial of isocaloric regimens showed that omega 6-PUFAs decreased hepatic fat, while a higher fat diet increased thin liver fat (Oliveira et al., 2016). A meta-analysis RCT or omega 6-PUFA analysis showed a comparable rise in overweight SFAs or omega 6-PUFAs, leading to a substantial increase in visceral fat when opposed to PUFA but no consistent significant effect was reported on insulin resistance (Jiang et al., 2005).

In summary, different types of fats have varied impacts on NAFLD and NASH, therefore, a reduction in total fat consumption is not a simple solution (Miele et al., 2009). The conventional dietary pattern is based on the high consumption of olive oil, nuts, fruits and legumes, vegetables, and seafood, as well as a reduced consumption of meat, meat products, and sugars (wine in moderation) (Kikuchi et al., 2014). In comparison to the reduced-fat lifestyle, which can contain equal to 30% fat, the nutrition has

40% fat, particularly MUFA and omega-3 PUFA. Furthermore, it has been demonstrated that MUFAs improve plasma lipids. Moreover, it's been shown that the Mediterranean diet improves metabolic signatures (Chai et al., 2001) and reduces the risk of heart disease and diabetes, two important consequences for individuals having NAFLD (Kwok et al., 2016).

Surprisingly, one of the Mediterranean diet element is avoiding food industrializing and high-sugar foods consumption. Glycation products (AGEs) are a diverse group of non-enzymatic compounds which are synthesized endogenously and may be ingested as a result of protein, lipid, and nucleic acid glycation (Jia et al., 2015; Moschen & Tilg, 2008). Diabetes and other metabolic diseases have indeed been linked to AGEs. They increase in type 2 diabetes, and NASH patients, and have been shown to be positively associated with insulin resistance and negatively associated with adiponectin (Schugar & Crawford, 2012).

The role of micronutrients

There is preliminary evidence to suggest that oxidative stress is linked to NASH, and that antioxidants are capable of decreasing the progression of the disease in preclinical studies. However, there is no data proving that the use of antioxidants can treat or prevent NASH in humans (Hu et al., 2012). With the goal of gaining a better understanding of NAFLD (nonalcoholic fatty liver disease), 3.471 subjects from the cross-sectional study including NAFLD patients were studied. A negative relationship and an inverse correlation was observed between males who have BMI and their sub - group (Zivkovic et al., 2007). Another cross-sectional research confirmed this result, demonstrating a substantial positive relationship between insufficient vitamin C consumption with NAFLD in the male population (Chung et al., 2014). However, several investigations found no such a link (Inzucchi et al., 2012).

In a large cross-sectional population-based study conducted in Shanghai using MRS-diagnosed NAFLD, a negative correlation was found between vitamin C, vegetables, legumes, and fruits intake and NAFLD frequency. According to this study, those who consumed this food had a lower incidence of non-alcoholic fatty liver disease (NAFLD) regardless of their body mass index (BMI) or other health conditions (De Backer et al., 2019).

Choline has been a critical component of cell membranes and is needed for the production of phospholipids, which are important for cell survival. In a cross-sectional research, the lack of choline has been associated with poorer postmenopausal female fibrosis and is more frequent in yolks and sources of animal protein (Duarte et al., 2014). Researchers have shown that vitamin D has antioxidant, anti-inflammatory, and anti-fibrotic properties and Vitamin D insufficiency has been linked to human NAFLD. A meta analysis of observational studies revealed that NAFLD patients are more prone to have vitamin D deficiency than the control group (Westerbacka et al., 2005). However, vitamin D deficiency was not linked to steatosis grade or insulin resistance in studies using the NASH cohort (Santos et al., 2013). Thus, the role of vitamin D in human NAFLD is unclear. Vitamin D insufficiency is common in Europe, with the least intake in Spain (44 I.U./day for women) and the highest in Finland (330 I.U./day for males) (Bozzetto et al., 2012).

Exercise and NAFLD

NAFLD affects a variety of pathways involved in the disease's development. Exercise has been proven to be helpful in the prevention and treatment of NAFLD. Exercise, in conjunction with dietary modifications, may decrease the severity of NAFLD via weight loss. In previous trials, people with steatosis who lost 5% of their body weight via exercise and diet had lower aminotransferase levels for at least 15 months following treatment. Some research focused only on the direct benefits of exercise on NAFLD, independent of whether the participants lost weight. Individuals with NAFLD who participated in low- and moderate-intensity aerobic exercise saw a reduction in hepatic enzyme levels and improved insulin sensitivity (Ma et al., 2013; Nabavi et al., 2014).

A specific resistance training program done three times per week for eight weeks was shown to be helpful in reducing intrahepatic lipid levels in people with nonalcoholic fatty liver disease (NAFLD) (Buss et al., 2015). Also, increasing muscle mass and strength while boosting insulin sensitivity is included in this kind of physical exercise. More importantly, aerobic exercise's effects on NAFLD are mostly mediated by two molecular processes: the activating of the lipoprotein receptor (ADR) and the adrenergic receptor (Velasco et al., 2014). Studies show that exercising on a regular basis can help break this cycle by improving glucose control and lipid oxidation in striated muscle, by increasing the expression and stimulation of the GLUT-4 glucose transporter, which in turn facilitates the transport of glucose into the muscle, and thus helps insulin and lipolysis occur in a positive manner. Increasing circulatory fatty acid and glucose intake may attenuate the consequences of insulin-stimulated de novo lipogenesis in the liver.

One theory about the relative roles of aerobic and resistance exercise in building muscular strength and muscle intracellular triglyceride synthesis is that resistance training appears to raise the level of F.A. metabolites, while increasing muscle intracellular triglyceride synthesis. Moreover, serve as an anti-inflammatory

agent in the presence of I.R. Thus, exercising may also benefit those who have NAFLD since it may help reduce the inflammatory state. A large portion of this may be attributed to myokines (cytokines and other peptides produced by muscle fibers and released into the bloodstream) and their paracrine and endocrine effects (Sanyal et al., 2010). It has been suggested that these molecules, which are generated during muscle contraction, have anti-inflammatory effects both directly and indirectly (by interfering with fat metabolism) (Attar & Van Thiel, 2013; Ji et al., 2014).

Oxygen and glycolytic muscle contraction both induce IL-6 production, and thus, it may be thought of as a myokine which also serves as a lipid-oxidation and glucose-consumption activator (Jiang et al., 2014). Individuals with NAFLD, according to cross-sectional research, engage in less physical activity than controls (Aguirre et al., 2014; Jiang et al., 2014), and are also more susceptible to fatigue. Furthermore, only physical activity surveys have been used to evaluate and describe activity levels in people with NAFLD. Importantly, surveys are subject to memory and impulsiveness discrimination and are inefficient at assessing physical activity frequency, duration, and intensity (Chen et al., 2015; Faghihzadeh et al., 2014).

The discrepancy among quantitative and subjective evaluations highlights the essential need of properly quantifying physical activity in therapeutic treatment. Exercise is important for metabolic control and is often recommended for people with NAFLD, usually in combination with weight loss and dietary modifications. While physical activity and exercising are recommended as part of NAFLD treatment, no meta analyses with appropriate effect size have really been conducted to help healthcare practitioners in prescribing exercise regimens or establishing physical activity guidelines for these people. Prospective studies show that individuals who live an active lifestyle had a lower risk of developing insulin resistance, impaired glucose tolerance, or type 2 diabetes (Gunji et al., 2009; Seitz et al., 2015).

Further, it has been demonstrated that fatty acid influx and cytokine and adipokine synthesis promote liver lipid accumulation, insulin resistance, and inflammation but the precise mechanism by which visceral fat exerts its detrimental effects on liver metabolism, fibrosis, and inflammation remains unknown (Suzuki et al., 2007). There is not much data on exercise and NAFLD, including the influence of exercise on inflammation (a key mediator of NAFLD development), the effect of exercise on the gut microbiota, and the effect of exercise on appetite. However, given that people with NAFLD are almost twice as likely as those without to develop cardiovascular disease (Sookoian et al., 2014), the beneficial effects of exercise on cardiovascular function (Dunn et al., 2012) should be studied further. Indeed, it is possible that the main benefit of exercise in NAFLD is to the cardiovascular system, rather than the liver.

Conclusion

Changes in health conditions such as nutrition and physical exercise will be the first line of therapy for NAFLD and NASH. Overall, any healthy diet (low fat, low carbohydrate, Mediterranean, etc.) that results in calorie restriction and is tolerated by the patient should be encouraged and endorsed. Changing the nutritional content of one's food without necessarily decreasing one's caloric intake may be a more realistic option for people who have difficulty with calorie restriction, The advantage to liver function is less apparent than the benefit to weight reduction, but both are beneficial. Losing weight is important in people with NASH, since a 7% body weight is linked with a major clinical improvement in liver function. Exercising has a substantial, albeit non-significant, effect on the value of fat deposited in the liver (vs. weight loss).

What is already known on this subject?

NAFLD, a general term that describes several diseases caused by hepatic fat deposition such as hepatic steatosis (HS) and nonalcoholic steatohepatitis (NASH), includes the many conditions that are related to fat accumulation in the liver.

What this study adds?

Although exercise has significant cardiovascular advantages, it is likely that the most beneficial use of exercise will be in conjunction with dietary changes, whether in NAFLD or NASH. Taken altogether, this data shows the critical nature of lifestyle modification as the main treatment for NAFLD, NASH, and other chronic illnesses. Instead of arguing whether lifestyle modification is a successful clinical treatment approach, the issue now is how to incorporate it into routine clinical care.

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Compliance with ethical standards

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