

The role of physical exercise and diet in the treatment of non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is characterized by an accumulation of hepatic fat, diagnosed histologically or radiologically (ultrasound), in the absence of a secondary cause of steatosis, especially alcohol consumption. Its prevalence is estimated to be approximately 25%. This high prevalence is correlated with the risk factors attributed to the metabolic syndrome. Non-alcoholic steatohepatitis (NASH) is a progressive form of NAFL and it can lead to end-stage liver disease in some patients. Once diagnosed, lifestyle changes must be initiated to lower hepatic fat accumulations in the liver. Physical exercise and diet play the most important role in achieving the desired weight loss goal.

Keywords: non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, high-intensity interval training, weight loss

Introduction

Non-alcoholic fatty liver disease (NAFLD) was first described in 1980. It is the most common liver disorder in Western industrialized countries. Worldwide, NAFLD has a reported prevalence of 6 to 35 percent (median 20 percent) [1], representing the second leading pathology in patients that await liver transplantation [2] and the third leading cause of hepatocellular carcinoma (HCC) in the United States [3].

NAFLD is a general term that encompasses 2 subsets of patients: individuals with nonalcoholic fatty liver (NAFL), which is defined by the presence of at least 5% hepatic steatosis without evidence of hepatocellular injury, and individuals with nonalcoholic steatohepatitis (NASH), which is defined by the presence of at least 5% hepatic steatosis and inflammation with hepatocellular injury (e.g. ballooning), with or without fibrosis [4]. Further disease progression among NASH patients involves development of fibrosis, cirrhosis, and cirrhosis related complications such as hepatocellular carcinoma and end-stage

liver disease [5] (Figure 1).

NMR Spectroscopy or MRI can be also diagnostic.

The growing prevalence of NAFLD has a direct association with the increasing prevalence of the metabolic syndrome. Risk factors for these related conditions include insulin resistance, type 2 diabetes mellitus, metabolic syndrome, obesity, hypertension and dyslipidemia [1,6]. Cardiovascular disease is the leading cause of death in NAFLD [7]. When diagnosing NAFLD, it is essential to exclude the liver's alcoholic steatosis. Alcohol consumption is considered significant when it is greater than >30 g/d in men and >20 g/d in women. Screening for NAFLD has been discussed, but the high direct and indirect cost of testing associated with low predictive values of the non-invasive tests does not justify the start of these kinds of programs. NASH, NAFLD's progressive forms, should be diagnosed in every patient, especially in those at risk which includes patients over 50 years and those with type 2 diabetes mellitus [4]. Patients with end-stage liver disease due to NASH have a risk of hepatocellular carcinoma.

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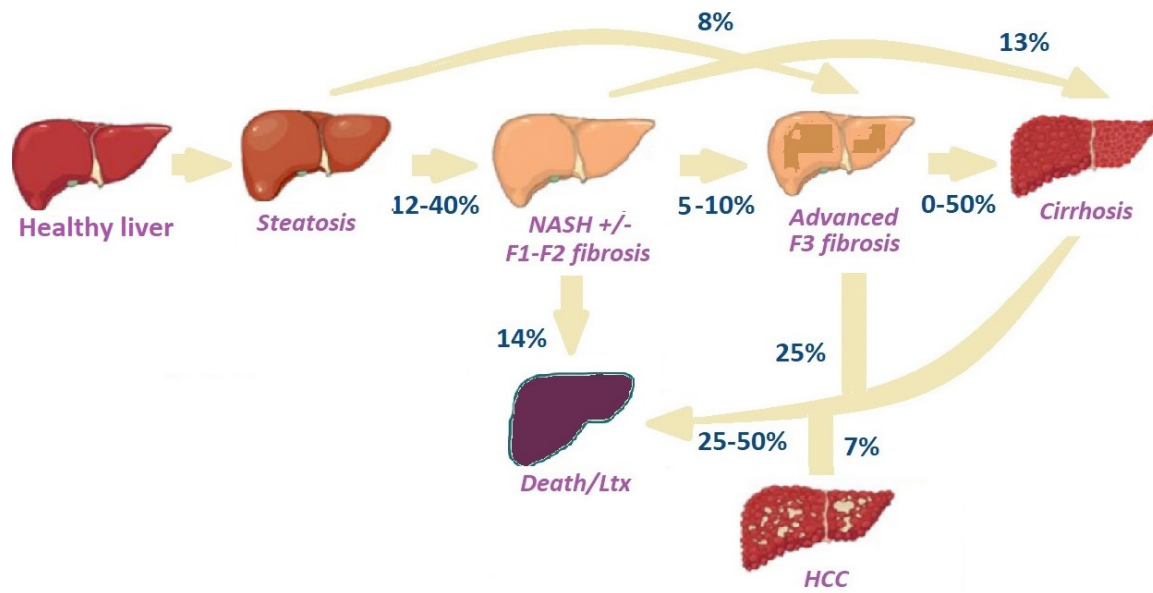


Figure 1. Representation of disease progression.

NASH: nonalcoholic steatohepatitis; HCC: hepatocellular carcinoma; LTx; liver transplantation (adapted after Day CP, European Association for the Study of the Liver, 2008).

With these aspects in mind, it comes as no surprise that the quintessential prevention and treatment of NAFLD is represented by weight loss and lifestyle changes. Due to the causal relationship of an unhealthy lifestyle with the development of NAFLD, these corrections are mandatory in all patients [4,8]. We aim to provide the latest recommendations regarding the use of optimum nutrition and physical exercise when treating NAFLD.

Dietary changes

Lifestyle changes are currently the only acceptable method to prevent and treat NAFL/NASH (Figure 2). Bodyweight, abdominal circumference, mean arterial pressure, fasting glucose levels, serum triglycerides and HDL (high-density lipoprotein) cholesterol levels are associated with the development of NAFLD in epidemiological studies [4,9]. A weight loss must be achieved to reduce the degree of steatosis. Weight loss also decreases the impact of the other risk factors. The degree of weight loss is independently associated with improvements in all NASH-related histologic parameters. It is currently indicated that a reduction in weight of $\geq 10\%$ leads to a resolution in non-alcoholic steatohepatitis and also a decrease in the grade of fibrosis. It is obvious that at least 5% reduction of body weight is necessary to improve NASH activity in the liver, while for fibrosis improvement even more than 10% are required [9,10].

Low calorie diet is the universally accepted way to lose weight. In obese patients, a 5-10% weight loss is the main goal of the lifestyle changes [4,11]. Current methods of weight loss include a hypocaloric diet and physical exercise. If the subjects do not meet their weight loss goals after six months of lifestyle interventions, including two visits for nutritional counseling, the bariatric surgery is recommended (except for patients with decompensated cirrhosis) [12]. A 3-10% loss of weight in lean patients with NAFLD has a significant effect in lowering the liver fat deposits.

The European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) guidelines currently recommend a 500-1000 kcal deficit/day, a weight loss target of 7-10% and a limit of alcohol consumption during this time [4].

The Mediterranean diet is the most cited diet for achieving the desired weight loss in NAFLD patients [13]. The foods that have a beneficial effect are fresh salads, tomatoes, eggplant, cucumber, cabbage, chickpeas, lentils, and beans, oranges and pomegranates, berries, figs, grapes, pistachios, almonds, peanuts, hazelnuts, walnuts, rice, oatmeal, sardines, mackerel, mussels, octopus, oysters, salmon, sea bass, shrimp, squid [14]. Olive oil is also regarded as a key component of this diet, while red wine, in small quantities, has also beneficial effects.

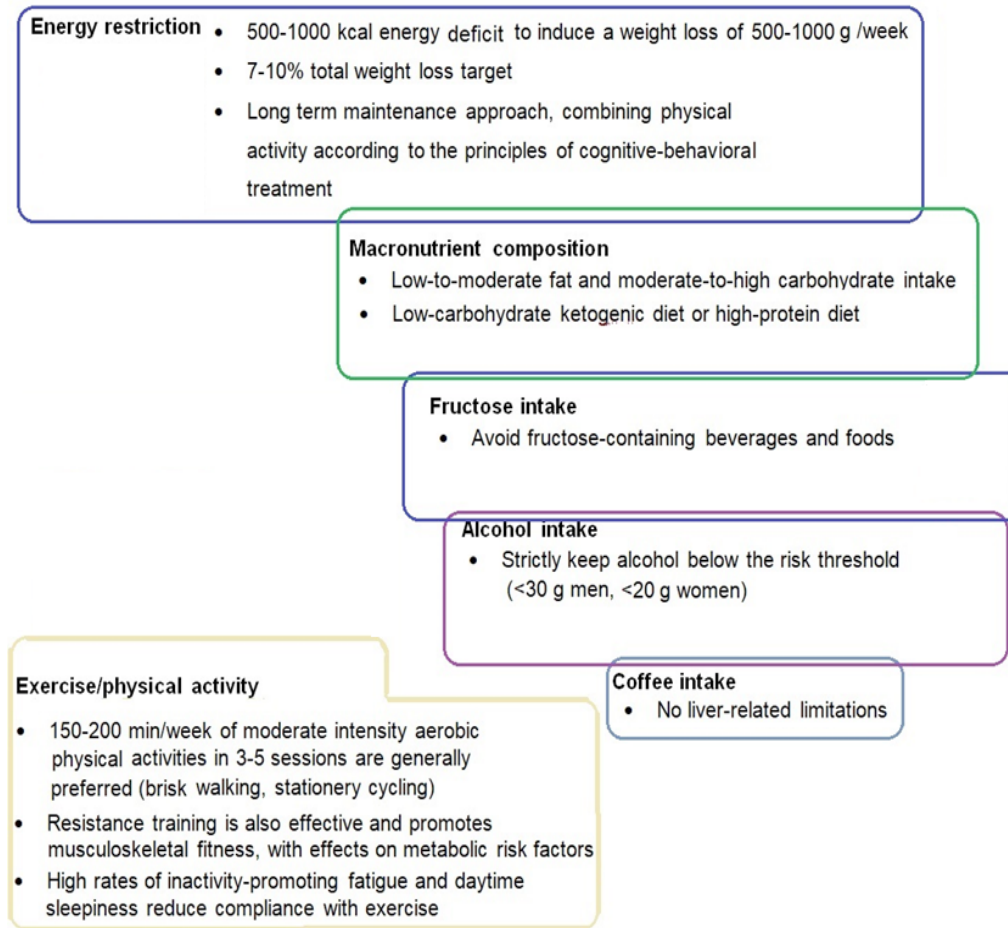


Figure 2. Elements of a comprehensive lifestyle approach to NAFLD therapy (image adapted after European Association for the Study of the Liver, Lifestyle approach NAFLD). American Association for the Study of the Liver (AASLD) guidelines have a similar approach regarding the calorie deficit. Only the NICE (National Institute for Health and Care Excellence) guidelines recommend a 600 kcal deficit/day, underlining the importance of low-fat diets for sustained weight loss.

The mechanisms underlying the beneficial effect of the Mediterranean diet include the reduction of blood lipids, the reduction of inflammatory and stress markers, improvement of insulin sensitivity, enhancement of endothelial function and antithrombotic function [15]. These effects are attributed to the bioactive ingredients such as polyphenols, monounsaturated and polyunsaturated fatty acids and fibers [16]. The diet contains approximately 40% of fats, which are especially monounsaturated or omega3-polyunsaturated [12].

During this period, patients should avoid processed meat, saturated fatty acids, sports drinks, sweetened tea, and juices with high sugar levels, because these have detrimental effects on the desired weight loss. It was

shown that the Mediterranean diet has a better effect on reducing liver steatosis when compared with a low-fat-high carbohydrate diet [17]. Alcohol consumption should also be minimized, due to its liver-damaging effects [6].

The Asia-Pacific diets underline the significance of the gradual calorie down-scaling. Crash diets are unsustainable and have a negative effect when treating NASH. Very-low calorie diets are also unsustainable and any specific regime is preferred to this approach [18].

Physical exercise

Sedentariness is one of the most important risk factors in NAFLD. Physical exercise is needed in most cases to achieve the desired weight loss. Resistance

exercise, high-intensity training or continuous aerobic training have fat-lowering effects on the liver [12]. High-intensity aerobic training has also been demonstrated to have improving effects on hepatic stiffness and restoring effects on Kupffer cell function, independent of fat loss.

EASL-EASD-EASO Guidelines currently recommend moderate-intensity aerobic training or exercise training, 150-200 min/week, in 3-5 sessions [4]. AASLD Guidelines indicate that the duration of the moderate-intensity training to last more than 150 minutes, while the NICE Guidelines indicate at least 45-60 minutes per day of moderate physical activity [11,19].

Golabi et al (2016) conducted a systematic review on studies that, using hydrogen-magnetic resonance spectroscopy (H-MRS) or liver biopsy evaluated the mass of intrahepatic triglycerides hepatic lipid deposits. They demonstrated a 30.2% reduction in hepatic fat as a result of exercise intervention. That number improved to 49.8% when dietary intervention was added to any type of physical exercise [20].

High-intensity interval training (HIIT) was associated with a reduction in liver fat, whole-body fat mass, ALAT and ASAT levels in patients with NASH and an increased early diastolic filling rates, its effects being superior to the standard approach with the moderate-intensity training [21]. High-intensity interval training is divided into aerobic and anaerobic training, also called sprint interval training. HIIT workouts generally combine short bursts of intense exercise with periods of rest or lower-intensity exercise [22]. Also, HIIT was proven to have a more beneficial effect on brachial artery vascular function, traditional cardiovascular disease factors, oxidative stress, inflammation and insulin sensitivity when compared to moderate-intensity continuous training [23].

All these benefits are lost if the patient does not continue to exercise [8]. Adhesion to the treatment is the key to success. A personalized training program is recommended whenever available.

The pharmacological approach is non-specific in patients with NASH. Several drugs including glucose-lowering agents (metformin, pioglitazone, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter-2 inhibitors), statins or antioxidants (Vitamin E) were tested to treat NAFLD [12,24]. The guidelines currently prefer pioglitazone. The current pharmacological treatment is not superior to lifestyle modifications [4]. Resmetirom are considered for patients with NAFLD disease, but currently, only preliminary data are available [12].

Bariatric surgery can be an option for the patients that do not respond to lifestyle changes or pharmacotherapy. It provides long-term results in weight reduction and metabolic complications [4].

NASH is the third leading indication for liver transplantation. Due to the fact that NASH patients have a higher rate of cardiovascular diseases and obesity and

a higher risk of post-transplant complications, graft non-function and graft loss are more common among these patients [25].

Conclusions

NAFLD is a common public health problem in the 21st century due to its high prevalence in the general population. NAFLD's clinical manifestations vary from silent disease to end-stage liver disease and HCC. Risk factors are attributed to the western diet and sedentariness. Chronic alcohol consumption must be excluded when diagnosing NAFLD. Liver lipid deposits can be assessed with spectroscopy, MRI or liver biopsy.

Lifestyle changes are considered as a primary approach for the management of NAFLD and its advanced forms. Weight loss can regress liver disease and the associated cardiovascular risk factors. A weight loss of more than 10% of the initial body weight can produce NASH resolution. Diets with a 500-1000 kcal deficit/day are currently recommended. The Mediterranean diet is currently cited to have the most beneficial effect on these patients. Physical exercise associated with the diet produces a better effect on lowering the liver's fat deposits. HIIT is preferred over moderate-intensity training. These benefits fade if physical exercise is discontinued. Other treatments are not superior to lifestyle changes.

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