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Treatment of Non-Alcoholic Fatty Liver Disease; Weight loss or Physical activity? An updated narrative mini review of most recent review articles

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Abstract

Non-Alcoholic Fatty Liver is the most common disease of the liver which may lead to steatohepatitis and cirrhosis if not treated properly. Most of the subjects with the disease are obese and insulin resistant while a very small percentage of them are lean. Current first line treatment focuses on weight loss and exercise. The purpose of this mini review is to update the audience with the latest information from Pubmed and Scopus on weight loss and exercise on NAFLD and evaluate the importance of each treatment separately and combined.

Keywords: Non-Alcoholic Fatty Liver Disease; Calories; Exercise; Insulin Resistance; Obesity.

1 Introduction

Non-Alcoholic fatty liver disease (NAFLD) is highly associated with obesity and insulin resistance (IR) (Loria et al. 2005). If untreated, it may lead to inflammation called steatohepatitis (NASH) and finally to cirrhosis which is the irreversible stage of the disease (Neuschwander-Tetri & Caldwell, 2003). Non-alcoholic fatty liver disease (NAFLD) has become a major global health burden, leading to an increased risk for cirrhosis, hepatocellular carcinoma, type-2 diabetes and cardiovascular disease. Treatment of NAFLD has been focused primarily on weight loss and exercise and secondarily on medication (Loria et al. 2005). The latest recommendation guidelines on diet and exercise from European Association of the Study of the Liver include a) a weight loss of 7-10 % with an adjustment of diet composition and b) any type of exercise (aerobic or resistance) (EASL, 2016). In the rest of the paper we will review the latest evidence on weight loss and exercise in the treatment of NAFLD.

1.1 Prevalence

The prevalence of the NAFLD may range from 9%-37% worldwide (Shen et al. 2003). Approximately 20% of the United States population suffers from non-alcoholic fatty liver, and the prevalence of this condition is increasing (Lazo et al. 2011).

1.2 Pathogenesis

The pathogenesis of the disease is not clear; however, IR is the most important factor for developing NAFLD. Insulin résistance increases fat breakdown from adipose tissue, which in turn, increases circulating free fatty acids having as a result the retention of lipids within the liver, called steatosis (Marchesini et al. 1999). De novo synthesis of fatty acids is also regulated by hyperinsulinemia and hyperglycemia. This is a result of genetic related

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factors such as sterol binding protein-1c and carbohydrate binding protein (Lambert et al. 2014).

1.3 Histology

The histologic features of steatohepatitis, which include steatosis, inflammation, ballooning hepatocyte necrosis, are similar to those of alcoholic liver disease (Neuschwander-Tetri & Caldwell, 2003). A new development system for grading and staging was recently developed by Alkhouri et al. (2012). The diagnosis of NASH was based on Brunt's criteria (Musso et al. 2011). Brunt criteria include the following parameters: Amount of fat: graded 1 to 3 according to the percentage of fatty droplets (1, 0%-33%; 2, 34-66%; 3, 67-100%).

1.4 Diagnosis

The diagnosis of NAFLD remains under-recognized, as most patients are asymptomatic until late stages of disease. Liver biopsy is the gold standard in diagnosing NAFLD and the most accurate tool for grading fibrosis however is invasive and carries the risk of complications (Loria et al. 2005). Even though significant liver disease can exist with normal levels of transaminases, increased levels of the hepatic enzymes aspartate aminotransferase and alanine aminotransferase (ALT) are usually very good predictors of the presence of NAFLD and NASH. Serum ALT levels can be found up to 10 times higher than normal in general population with fatty liver disease. The last few years, different non-invasive tests have been developed to estimate liver fibrosis (FibroTest) (Halfon et al. 2008) and simple steatosis (SteatoTest) (Ratziu et al. 2006). However, both of them have not been widely adopted (Schwenzer et al. 2009).

2 Treatment

2.1 Weight loss alone

A couple of studies (Huang et al. 2005; Nobili et al. 2008) in the past have shown that a weight loss program alone may improve the histological profile of the patients but without decrease in NAFLD. However, both studies concluded that a reduction of total body weight between 5%-10% would have the most benefits to these patients. Recently, a review by Hsu et al. (2017), showed that weight loss even alone is very crucial to the improvement of NAFLD and NASH. Similar results were also presented by another review one year ago (Hannah & Harrison, 2016). These diets included a 600-800 Kcal less of total energy requirements with a 40-45% of Carbohydrates, and <30% from Fat.

2.2 Exercise alone

Exercise alone has also been found to have positive results. Hallsworth et al (2011) found that after 8 wk (3 times per week lasting 45-60 min) of resistance-based exercise resulted in a reduction of liver lipids, and improvements of lipid oxidation, glucose control and insulin resistance. Hannah and Harrison (2016) also reported that physical activity without weight loss seems to decrease hepatic steatosis. More recently, a systematic review (Katsagoni et al. 2017) analyzed 20 RCTs with 1073 NAFLD patients. The authors concluded that exercise alone or combined with dietary intervention improves serum levels of liver enzymes and liver fat or histology. In addition, exercise has shown to exert beneficial effects on intrahepatic triglycerides even in the absence of weight loss. Moreover, regarding the type of exercise, aerobic compared to resistance exercise did not

yield any superior improvements on liver parameters, whereas moderate-intensity continuous training at a moderate to high volume was more beneficial compared to moderate-intensity continuous training or high-intensity interval training at a low-to-moderate volume (Katsagoni et al. 2017). Another met-analysis (Orci et al. 2016) reviewed 28 trials and the authors concluded that physical activity, independently from diet change, was associated with a significant reduction in intrahepatic lipid content. All review papers discussed above concluded that an 150-200 min of aerobic exercise per day for a minimum of 3 days is required in order to achieve a decrease hepatic steatosis. In addition, resistance training is also effective on reducing metabolic risk factors.

2.3 Weight loss and Exercise Combined

Most of the literature data supports the beneficial effects of weight loss and exercise in combination in the treatment of NAFLD. In 2012, a systematic review was conducted by Thoma et al. and analyzed 23 studies using diet modification, physical activity, or a combination of both. The authors concluded that lifestyle modifications that led to weight reduction and/or increased physical activity greatly reduced liver fat and improved insulin sensitivity. Two years later, a review by Schwenger and Allard (2014) summarized the effects of weight loss and exercise intervention studies in obese patients with NAFLD and showed that overall, lifestyle modification (diet and exercise) resulting in weight loss or increased physical activity can reduce liver enzymes and inflammation and improve liver histology, glucose control, and insulin sensitivity and lipid oxidation. Diet and exercise is also more effective in a recent systematic review (Golabi et al. 2016). In this review, eight studies with 433 participants were analyzed and the authors concluded that diet and exercise was more effective compared to exercise alone in reducing intrahepatic steatosis. Katsagoni et al (2017) also supported the above results in a systematic review of 1073 patients. She concluded that exercise combined with dietary intervention improves serum levels of liver enzymes and liver fat or histology. Moreover, lifestyle intervention that includes weight loss and exercise were strongly reported in another recent review as the primary therapy for the treatment of NAFLD and NASH (Romero-Gomez et al. 2017).

3 Conclusion

Lifestyle modification remains the cornerstone for the management of NAFLD and NASH. The evidence is clear that weight loss and exercise together exert the maximum effect in the treatment of NAFLD and NASH. A 7-10 % weight fat loss with 40-45% from carbohydrates, <30% from fat and the rest from protein should be the focus of the dietary treatment. Exercise regimen should include either aerobic (150 minutes 3 times per week) or resistance weight lifting. In cases that the above combination is available, even a weight loss or exercise program alone will still have a beneficial effect on the reduction of hepatic steatosis.

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