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http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **19**(3):225-228
doi: 10.2478/v10255-012-0027-z

Editorial

NONALCOHOLIC FATTY LIVER DISEASE – HOW TO MANAGE A "NEW" CARDIOVASCULAR RISK FACTOR?

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver injury, characterized by fatty infiltration that involves more than 5% of hepatocytes in the absence of alcohol consumption (or an intake of less than 20 g in women and 30 g in men). NAFLD includes a spectrum of disease from simple steatosis to nonalcoholic steatohepatitis (NASH), which can progress to liver cirrhosis and hepatocellular carcinoma.

Histological, NASH is defined by the presence of macrovesicular steatosis, lobular inflammation, and hepatocellular ballooning.

Epidemiology

The prevalence of NAFLD in the general population, assessed by ultrasonography is 20–30% in Europe and the Middle East, 15% in the Far East, and 16% in some studies of normal weight subjects without metabolic risk factors [1]. A surprisingly high prevalence of histological NAFLD has been described in apparently healthy living liver donors: 12-18% in Europe and 27-38% in the US. With sensitive technique such as MR spectroscopy, 34% of US adults have NAFLD [2]. Interestingly, 39% of newly identified cases of chronic liver disease in a US survey had NAFLD [3] which makes NAFLD/NASH one of the top causes of chronic liver disease in Western countries.

The most common cause of NAFLD is primary NAFLD associated with insulin resistance and its manifestations: obesity, visceral adiposity, type 2 diabetes mellitus, hypertriglyceridemia and arterial hypertension. Thus, up to 95% of obese persons and 75% of patients with type 2 diabetes mellitus are likely to have NAFLD [4].

Less common causes of hepatic steatosis and steatohepatitis are: disorders of lipid metabolism (abetalipoproteinemia, familial combined hyperlipidemia, lipodystrophy etc.), glycogen storage disease, drug toxicity (amiodarone, tamoxifen, methotrexate, corticosteroids, Highly Active Antiretroviral Therapy – HAART), total parenteral nutrition, starvation, hepatitis C virus infection, Wilson's disease, celiac disease, severe weight loss after bariatric surgery and environmental toxicity [5].

Auto-antibodies are frequently present in patients with NAFLD in the absence of autoimmune hepatitis and their occurrence is

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not associated with more advanced or severe histological features [6].

Complications

NASH significantly increases overall and liver-related mortality; cirrhosis, neoplasia, and cardiovascular disease are the main causes of death in patients with NASH. Epidemiologic studies have reported an increased incidence of adverse CV events in NAFLD subjects compared with the general population. Several studies have also shown a significant association between increased gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) levels and CV mortality over an average median of 12-years follow up, even after adjustment for typical CV risk factors and body mass index (BMI) [7].

In biopsy-proven NAFLD, steatosis was associated with increased carotid intima-media thickness and with carotid plaques [8]. Significant more severe carotid atherosclerosis occurred 5-10 years earlier in subjects with NAFLD than in those without [9]. One study reported a significant association between "vulnerable plaque" incidence and NAFLD in patients undergoing multislice CT for clinical suspicion of coronary artery disease [10].

Regarding endothelial dysfunction (the earliest detectable atherosclerotic CV alteration), studies have shown an independent association between impaired endothelium-dependent flow-mediated dilation (FMD) and NAFLD in both diabetic and non-diabetic patients cohorts [11]. In addition, lower FMD was observed in NASH compared with simple steatosis, again confirming the graded association of CV risk with the severity of NAFLD.

It is therefore imperative that future trials in NAFLD also aim to include measurements of a range of validated cardiac, metabolic, and inflammatory biomarkers linked to clinical outcomes, to serve as alternative objective measures of the change in NAFLD status and its associated cardio-metabolic phenotype [12].

Therapeutic management

Lifestyle intervention (weight loss, physical exercise, reduction of sedentary lifestyle and dietary changes) should be implemented as first-line therapy on a long-term basis in all patients with NAFLD/NASH, regardless of the severity of their liver disease [13]. The best results are obtained with a multidisciplinary yet personalized approach ("multi-factorial" intervention). Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necro-inflammation status [14]. Behavioral therapy could help and should be implemented whenever the required resources, which are considerable, are available.

Experimental and limited clinical data suggest that increasing omega-3 dietary supplementation may lead to both metabolic and histological improvements. There is no evidence that alcohol abstinence is beneficial for patients with NAFLD/NASH. In fact studies have shown an inverse association between modest wine drinking (less than a glass a day) and biochemical, ultrasonographic or histological evidence of NAFLD/NASH with protective effects on diabetes, IR, and features of the metabolic syndrome.

Pharmacologic therapy directed to the correction of concurrent metabolic disorders (statins, antihypertensive agents, antidiabetic drugs, etc.) should be given as needed, as NAFLD does not increase hepatotoxicity or

other side effects of these drugs. Pharmacologic therapy specifically aimed at improving the liver condition is indicated based on the potential for disease progression, the severity of fibrosis, and the potency of drugs to reverse or stop the progression of liver damage.

Glitazones are the only compounds having consistently shown some benefit in patients with NASH. Almost all studies have shown a reduction in aminotransferase levels and steatosis and an improvement in liver-cell injury and inflammation in short term administration. So, the American NAFLD treatment guidelines recommendations are that pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that the majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established [14].

Metformin had a beneficial effect on ALT in some [15] but not all the studies [16] and is not recommended for the treatment of NAFLD.

Urso-desoxycholic acid alone did not show a consistent biochemical and histological benefit at the dose of 13-15 mg/kg; higher doses (30 mg/kg) induced a significant reduction in aminotransferase values, although it is uncertain whether this translates into histological improvement.

In clinical trials, including the PIVENS trial [17], the use of vitamin E was associated with a decrease in aminotransferases, improvement in steatosis, inflammation and ballooning, and resolution of steatohepatitis in subjects with NASH. Vitamin E (α-tocopherol) administered at a daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis [14].

Other hepatoprotective agents such as betaine, pentoxifilline, or silibinin were not convincingly effective in randomized trials. Only preliminary uncontrolled trial results are available for omega-3 polyunsaturated fatty acids and sartans.

To summarize, there is currently no established pharmacological treatment for NAFLD, and lifestyle interventions such as increasing exercise, reducing dietary fat intake, and encouraging weight loss are the only recommended therapeutic strategies with proven benefit.

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