Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (**NAFLD**) is one of the causes of fatty liver, occurring when fat is deposited (steatosis) in the liver due to causes other than excessive alcohol use. NAFLD is the most common liver disorder in developed countries.[1][2]

NAFLD is related to insulin resistance and the metabolic syndrome and may respond to treatments originally developed for other insulin-resistant states (e.g. diabetes mellitus type 2) such as weight loss, metformin, and thiazolidinediones.[3] Up to 80% of obese people have the disease.[4] **Non-alcoholic steatohepatitis** (**NASH**) is the most extreme form of NAFLD, and is regarded as a major cause of cirrhosis of the liver of unknown cause.[5] Most people have a good outcome if the condition is caught in its early stages.[6]

A study using the National Health and Nutrition Examination Survey (NHANES) found a 30% rate of NAFLD in the United States between 2011 and 2012.[7]

1 Signs and symptoms

Most people with NAFLD have few or no symptoms. Patients may complain of fatigue, malaise, and dull right-upper-quadrant abdominal discomfort. Mild jaundice may be noticed although this is rare. More commonly NAFLD is diagnosed following abnormal liver function tests during routine blood tests. By definition, alcohol consumption of over 20 g/day (about 25 ml/day of net ethanol) excludes the condition.[3]

NAFLD is associated with insulin resistance and metabolic syndrome (obesity, combined hyperlipidemia, diabetes mellitus (type II), and high blood pressure).[3][5]

2 Causes

NAFLD can also be caused by some medications:[3]

- Amiodarone
- Antiviral drugs (nucleoside analogues)
- Aspirin rarely as part of Reye's syndrome in children
- Corticosteroids
- Methotrexate
- Tamoxifen
- Tetracycline

2.1 Soft drinks

Soft drinks have been linked to NAFLD due to high concentrations of fructose, which may be present either in high-fructose corn syrup or, in similar quantities, as a metabolite of sucrose. The quantity of fructose delivered by soft drinks may cause increased deposition of fat in the abdomen.[8][9]

2.2 Genetics

Native American men have a high prevalence of non-alcoholic fatty liver disease. Two genetic mutations for this susceptibility have been identified, and these mutations provided clues to the mechanism of NASH and related diseases.

Polymorphisms (genetic variations) in the single-nucleotide polymorphisms (SNPs) T455C and C482T in APOC3 are associated with fatty liver disease, insulin resistance, and possibly hypertriglyceridemia. 95 healthy Asian Indian men and 163 healthy non-Asian Indian men around New Haven, Connecticut were genotyped for polymorphisms in those SNPs. 20% homogeneous wild both loci. Carriers of T-455C, C-482T, or both (not additive) had a 30% increase in fasting plasma apolipoprotein C3, 60% increase in fasting plasma triglyceride and retinal fatty acid ester, and 46% reduction in plasma triglyceride clearance. Prevalence of non-alcoholic fatty liver disease was 38% in carriers, 0% wild (normal). Subjects with fatty liver disease had marked insulin resistance.[10]

3 Pathophysiology

NAFLD is considered to cover a spectrum of disease activity. This spectrum begins as fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function, but by varying mechanisms and possible insults to the liver may also progress to become non-alcoholic steatohepatitis (NASH), a state in which steatosis is combined with inflammation and fibrosis (steatohepatitis). NASH is a progressive disease: over a 10-year period, up to 20% of patients with NASH will develop cirrhosis of the liver, and 10% will suffer

death related to liver disease.[11] Cigarette smoking is not associated with an increased risk of developing NASH.

The exact cause of NAFLD is still unknown. However, both obesity and insulin resistance probably play a strong role in the disease process. The exact reasons and mechanisms by which the disease progresses from one stage to the next are not known.

One debated mechanism proposes a "second hit", or further injury, enough to cause change that leads from hepatic steatosis to hepatic inflammation. Oxidative stress, hormonal imbalances, and mitochondrial abnormalities are potential causes for this "second hit" phenomenon.[3]

4 Diagnosis

Common findings are elevated liver enzymes and a liver ultrasound showing steatosis. An ultrasound may also be used to exclude gallstone problems (cholelithiasis). A liver biopsy (tissue examination) is the only test widely accepted as definitively distinguishing NASH from other forms of liver disease and can be used to assess the severity of the inflammation and resultant fibrosis.[3]

Non-invasive diagnostic tests have been developed, such as FibroTest, that estimates liver fibrosis,[12] and SteatoTest, that estimates steatosis,[13] however their use has not been widely adopted.[14] Apoptosis has been indicated as a potential mechanism of hepatocyte injury as caspase-cleaved cytokeratin 18 (M30-Apoptosense ELISA) in serum/plasma is often elevated in patients with NASH and tests based on these parameters have been developed;[15] however, as the role of oncotic necrosis has yet to be examined it is unknown to what degree apoptosis acts as the predominant form of injury.[16][17]

Other diagnostic tests are available. Relevant blood tests include erythrocyte sedimentation rate, glucose, albumin, and kidney function. Because the liver is important for making proteins used in coagulation some coagulation related studies are often carried out especially the INR (international normalized ratio). Blood tests (serology) are usually used to rule out viral hepatitis (hepatitis A, B, C and herpes viruses like EBV or CMV), rubella, and autoimmune related diseases. Hypothyroidism is more prevalent in NASH patients which would be detected by determining the TSH.[18]

It has been suggested that in cases involving overweight patients whose blood tests do not improve on losing weight and exercising that a further search of other underlying causes be undertaken. This would also apply to those with fatty liver who are very young or not overweight or insulin-resistant. In addition those whose physical appearance indicates the possibility of a congenital syndrome, have a family history of liver disease, have abnormalities in other organs, and those that present with moderate to advanced fibrosis or cirrhosis.[19]

5 Management

No pharmacological treatment has received approval as of 2015.[20] Some studies suggest diet, exercise, and antiglycemic drugs may alter the course of the disease. General recommendations include improving metabolic risk factors and reducing alcohol intake.[3][21] While many treatments appear to improve biochemical markers such as alanine transaminase levels, most have not been shown to reverse histological abnormalities or reduce clinical endpoints.[3]

5.1 Nutrition

Treatment of NAFLD typically involves counseling to improve nutrition and consequently body weight and composition. Diet changes have shown significant histological improvement.[22] Specifically, avoiding food containing high-fructose corn syrup and trans-fats is recommended.[23] A systematic review and meta-analysis found that omega-3 fatty acid supplementation in those with NAFLD/NASH using doses approaching or higher than 1 gram daily (median dose 4 grams/day with median duration 6 months treatment) has been associated with improvements in liver fat.[24][25] The best dose of omega-3 fatty acids for individuals with NAFLD/NASH is unclear.[24]

Epidemiological data have suggested that coffee consumption may be associated with a decreased incidence of NAFLD and may reduce the risk of liver fibrosis in those who already have NAFLD/NASH.[24] Olive oil consumption, as part of the Mediterranean diet, is also a reasonable dietary intervention; the optimal dose of olive oil supplementation for people with NAFLD/NASH has not been well-established.[24] Few studies have been performed to evaluate the respective impact of a diet rich in avocados, red wine, tree nuts, or tea in people with NAFLD/NASH.[24] However, limited evidence suggests that avocados may improve other areas of cardiovascular health (i.e., lipid profile) and their addition to a balanced diet is reasonable.[24] Red wine consumption (in modest amounts) is likely safe and may improve insulin resistance but definitive studies are lacking.[24]

5.2 Exercise

Gradual weight loss may improve the process in obese patients; rapid loss may worsen NAFLD. Specifically, walking or some form of aerobic exercise at least 30–45 minutes daily is recommended.[23] The negative effects of rapid weight loss are controversial: the results of a meta-analysis showed that the risk of progression is very low.[26]

5.3 Medication

Insulin sensitizers (metformin and thiazolidinediones) are commonly used for insulin resistance in those with NAFLD.[27] Improvements in liver biochemistry and histology in patients with NAFLD through treatment with statins have been observed in numerous cases, although these studies were carried out on a relatively small sample of patients.[28] Statins have also been recommended for use in treating dyslipidemia for patients with NAFLD. Treatment with pentoxifylline has demonstrated improvements in the histological appearance of fatty liver tissue under the microscope in many small trials.[27]

5.4 Surgery

A recent meta-analysis presented at the Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) reported that weight-loss surgery leads to improvement and or resolution of NASH in around 80% of patients.[29]

6 Epidemiology

The percentage of people with non-alcoholic fatty liver disease ranges from 9 to 36.9% in different parts of the world.[30][31][32] Approximately 20% of the United States population have non-alcoholic fatty liver, and the number of people affected is increasing.[33] This means about 75 to 100 million people in the United States are affected.[34]

The rates of non-alcoholic fatty liver disease is higher in Hispanics, which can be attributed to high rates of obesity and type 2 diabetes in Hispanic populations.[35] Non-alcoholic fatty liver disease is also more common among men than women in all age groups until age 60, where the prevalence between sex equalize. This is due to the protective nature of estrogen.[36] Fatty liver and NASH occur all ages, with the highest rates in the 40- to 49-year-old age group. It is the most common liver abnormality in children ages 2 to 19.[37]

7 Children

Pediatric nonalcoholic fatty liver disease (NAFLD) was first reported in 1983.[38] It is currently the primary form of liver disease among children.[39] NAFLD has been associated with the metabolic syndrome, which is a cluster of risk factors that contribute to the development of cardiovascular disease and type 2 diabetes mellitus. Studies have demonstrated that abdominal obesity and insulin-resistance in particular are thought to be key contributors to the development of NAFLD.[40][41][42][43][44] Because obesity is becoming an increasingly common problem worldwide, the prevalence of NAFLD has been increasing concurrently.[45] Moreover, boys are more likely to be diagnosed with NAFLD than girls with a ratio of 2:1.[46][47] Studies have suggested that progression toward a more advance stage of disease among children is dependent on age and presence of obesity.[42] This finding is consistent with previous studies in adults demonstrating the same association between age and obesity, and liver fibrosis.[48][49] Early diagnosis of NAFLD in children may help prevent the development of liver disease during adulthood.[42][50] This is challenging as most children with NAFLD are asymptomatic with few showing abdominal pain.[50] Currently, liver biopsy is considered the gold standard for diagnosing NAFLD.[39] However, this method is invasive, costly and bears greater risk for children, and noninvasive screening and diagnosing methods would have significant public health implications for children with NAFLD.[39] The only treatment shown to be truly effective in childhood NAFLD is weight loss.[51][52]

8 Research

Many drug candidates are in advanced clinical studies as : elafibranor,[53] obeticholic acid.[54]

9 See also

- Fatty liver (includes both non-alcoholic and alcoholic liver disease)
- Alcoholic liver disease

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11 Further reading

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12 External links

- Medscape article on NASH.
- MEDICINENET article on Steatosis.
- NIH page on Nonalcoholic Steatohepatitis
- British Medical Journal article on the diagnosis and initial management of non-alcoholic fatty liver disease

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