REVIEW ARTICLE

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) — EVALUATION & MANAGEMENT

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is currently widely accepted as a spectrum ranging from isolated fatty liver to nonalcoholic steatohepatitis(NASH). Although isolated fatty liver is thought to have a generally benign histopathological course, it appears that NASH may progress to cirrhosis at a rate of ~10% over a 20-year period. A small but significant group of patients with the more aggressive form of fatty liver, nonalcoholic steatohepatitis (NASH), are at risk of developing cirrhosis and hepatocellular carcinoma. As patients are generally asymptomatic, often their disease goes unrecognized. Therapies aimed at improving NAFLD are urgently needed. This review will focus on evaluation and current management of this disease.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently widely accepted as a spectrum ranging from isolated fatty liver to NASH. Although isolated fatty liver is thought to have a generally benign histopathological course, it appears that NASH may progress to cirrhosis at a rate of ~10% over a 20-year period. [1]

Zelman first described the existence of liver disease in very obese men in 1952. [2] Subsequently, abnormal liver function tests and liver morphology in obese patients was observed and these parameters improved with weight loss.[3] It was not until 1980 that the term nonalcoholic steatohepatitis (NASH) was coined by Ludwig and colleagues, who first described the pathological changes still used today.[4] NASH affects 2 to 5 percent of Americans. An additional 10 to 20 percent of Americans have "fatty liver" that is fat in their liver without inflammation or liver damage. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature in NASH is fat in the liver, along with inflammation and damage.

Definition

Fatty inflammation of the liver in people who do not abuse alcohol. It is typically a chronic condition that causes no symptoms or very mild symptoms but can sometimes cause progressive scarring and cirrhosis of the liver.

NAFLD appears to be the liver component of a metabolic syndrome.

The combination of the findings of obesity, hyperinsulinemia, insulin resistance, diabetes, hypertriglyceridemia, and hypertension has been referred to as a "metabolic syndrome" or "syndrome X". People with syndrome X also have a liver disease. In fact, people with syndrome X often have more advanced forms of NAFLD – i.e. fibrosis or cirrhosis.

Pathophysiology

Fatty liver is the accumulation of triglycerides and other fats in the liver cells. In some patients, this may be accompanied by hepatic inflammation and liver cell death (steatohepatitis). 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 outright inflammation of the liver. When inflammation occurs in this setting, the condition is then called NASH. 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. NASH may be the result of 2 liver insults. With the initial insult, macrovesicular steatosis occurs which is a manifestation of excessive triglyceride accumulation in the liver. Insulin resistance and subsequent hyperinsulinemia appear to lead to alterations in the hepatic pathways of uptake, synthesis, degradation,

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and secretion of free fatty acids and ultimately to accumulation of lipids in the hepatocytes. These changes seem to make the liver susceptible to a second insult, resulting in an inflammatory response and progression of liver damage. Oxidative stress, mainly caused by mitochondrial dysfunction and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) are believed to play an important role for this "second hit" phenomenon in the progression of liver damage in NAFLD. Potential oxidative stressors include hepatic iron, leptin, antioxidant deficiencies and intestinal bacteria. Hepatocyte apoptosis, an organized form of cell death, has been identified as a potential key component of the second insult involved in NAFLD progression. One global hypothesis for the pathogenesis of NASH is the "multi-hit hypothesis,"with metabolic syndrome playing a major role, due to insulin resistance and the

proinflammatory process mediated by different proteins and immune components. The identities of the multiple "hits" are different in each patient and largely undefined at present.

Potential pathophysiological mechanisms include the following:

(1) decreased mitochondrial fatty acid beta-oxidation(2) increased endogenous fatty acid synthesis or enhanced delivery of fatty acids to the liver, and (3) deficient incorporation or export of triglycerides as very low-density lipoprotein. NASH is not simply obesity that affects the liver. NASH is the most extreme form of NAFLD, and is regarded as a major cause of cirrhosis of the liver of unknown cause.

Causes

The exact cause of NAFLD is still unknown.

The most common association with fatty liver disease is metabolic syndrome. There is evidence to suggest the presence of an association between insulin resistance and the development of NAFLD. In this situation, in spite of the body making adequate insulin, the ability of cells to adequately use that insulin to metabolize glucose is abnormal. The relative excess of glucose is then stored as fat and can accumulate in the liver. This includes type II diabetes, obesity, and hypertriglyceridemia. Other factors, such as drugs (eg, amiodarone, tamoxifen, methotrexate), alcohol, metabolic abnormalities (eg, galactosemia, glycogen storage diseases, homocystinuria, tyrosinemia), nutritional status (eg, overnutrition, severe malnutrition, total parenteral nutrition [TPN], starvation diet), or other health problems (eg, celiac sprue, Wilson's disease, haemachromatosis) may contribute to fatty liver disease.

Symptoms

Nonalcoholic steatohepatitis or NASH is a common, often "silent" liver disease with few or no symptoms. Symptoms—such as fatigue, weight loss and weakness develops once the disease is more advanced or cirrhosis develops. The progression of NASH can take years, even decades. NASH can slowly worsen, causing scarring or "fibrosis" to appear and accumulate in the liver. As fibrosis worsens, cirrhosis develops with complications that include variceal bleeding, ascites, encephalopathy and other features of liver failure.

Many patients with NASH are obese have elevated blood lipids, such as cholesterol and triglycerides, and many have diabetes or pre-diabetes, but not every obese person or every patient with diabetes has NASH. Furthermore, some patients with NASH are not obese, do not have diabetes, and have normal blood cholesterol and lipids. There are reports of lean NASH families. NASH can occur without any apparent risk factor and can even occur in children.

Diagnosis

NASH is usually first suspected in a person who is found to have elevations in liver tests that are included in routine blood test panels, such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST). When further evaluation shows no apparent reason for liver disease (such as medications, viral hepatitis, or excessive use of alcohol) and when x- rays or imaging studies of the liver show fat, NASH is suspected. These levels may be elevated as much as 10-fold. However, the AST and ALT levels may be normal in some patients with fatty liver or NASH. In the absence of cirrhosis, an AST-to-ALT ratio of greater than 2 suggests alcohol use, whereas a ratio of less than 1 may occur in patients with NASH.

Noninvasive studies, such as ultrasound, CT scan and MRI, may identify the presence of a fatty liver. However, these imaging techniques cannot distinguish between benign steatosis and steatohepatitis. Benign steatosis may be focal or diffuse, whereas steatohepatitis is usually diffuse.

The diagnosis of fatty liver or NASH can be established only with a liver biopsy. Specific histologic findings include the following: (1) steatosis, which usually is macrovesicular but may be microvesicular or mixed; (2) inflammatory infiltrates consist of mixed neutrophilic and mononuclear cells, and portal

infiltrates usually are not seen (unlike in hepatitis C); (3) ballooning degeneration; and (4) fibrosis. NASH is diagnosed when liver biopsy shows fat along with inflammation and damage to liver cells. If the tissue shows fat without inflammation and damage, simple fatty liver or NAFLD is diagnosed. Currently, no blood tests or scans can reliably provide this information.

As there are no validated biomarkers of response to treatment, one must rely on histological assessment of a liver-biopsy specimen for this purpose. The activity score for nonalcoholic fatty liver disease quantifies the severity of steatosis, hepatocellular ballooning, and inflammation — the key histological components of the disease.[5]

Treatment

Currently, no specific therapies for NASH exist. Targets for therapy are insulin resistance and oxidative stress.The most important recommendations given to persons with this disease are

- reduce their weight (if obese or overweight)
- follow a balanced and healthy diet
- increase physical activity
- avoid alcohol
- avoid unnecessary medications

These are standard recommendations, but they can make a difference. They are also helpful for other conditions, such as heart disease, diabetes, and high cholesterol

Supplementation with the natural form of vitamin E (800 IU/day) has beneficial effects in patients with nonalcoholic steatohepatitis (NASH), but pioglitazone's benefits are less clear. Vitamin E was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes. There was no benefit of pioglitazone over placebo for the primary outcome; however, significant benefits of pioglitazone were observed for some of the secondary outcomes[6]

The first step in treating fatty liver disease is what causes it like obesity, prediabetes, and frank diabetes. Always aim for diet and exercise. Ideally, a 10% reduction in weight, which has been correlated with an improvement in insulin resistance and histology. Treatment should be started with vitamin E 800 IU/day. Patients who have more advanced disease, where the disease is progressing and they are not able to lose the weight could be put on a trial of pioglitazone.

Administration of pioglitazone led to metabolic and histological improvement in subjects with nonalcoholic steatohepatitis. Larger controlled trials of longer duration are warranted to assess the long-term clinical benefit of pioglitazone.[7] A recent multicenter trial showed a reduction in hepatic steatosis but no improvement in markers of cell injury after a year of rosiglitazone therapy.[8] The value of these drugs remains uncertain. Although clearly statins appear safe for the treatment of hyperlipidemia in NAFLD patients, the issue of whether or not they are efficacious in the treatment of NASH is more uncertain. Orlistat has been the most studied weight loss medication as a potential treatment for NASH but falls short as a treatment panacea for NASH.

Prognosis

The process can stop and in some cases, reverse on its own without specific therapy with weight loss and/or stopping alcohol use or NASH can slowly worsen, causing scarring or "fibrosis" to appear and accumulate in the liver. As fibrosis worsens, cirrhosis develops.

NASH ranks as one of the major causes of cirrhosis in America, behind hepatitis C and alcoholic liver disease. Long-term natural history studies of patients with NAFLD who undergo repeat biopsies have shown that 30% progress, 30% remain stable, and 30% improve over a 3-year period without pharmacologic intervention.[9] Abnormal glucose tolerance testing is an independent risk factor for progression of NASH.[10]

Complications

A study conducted by researchers at the Cleveland Clinic finds that patients suffering from cirrhosis preceded by nonalcoholic steatohepatitis are at an equal risk of developing hepatocellular carcinoma than those who develop cirrhosis resulting from hepatitis C virus (HCV). This study established that NASH-induced cirrhosis is a much greater risk factor for HCC than previously thought. The most significant factor recognized in this study was that of alcohol intake. It supports emerging data that alcohol intake, even in 'social' quantities, may potentially increase the risk of HCC development in NASH- and HCV-cirrhotic patients compared with non-drinkers [11]

Conclusion

The global epidemic of obesity as a result of sedentary life styles, increased processed carbohydrates has led to a dramatic increase in the prevalence of the generally asymptomatic NAFLD. In the subset of these patients with NASH, accumulation of fat in hepatocytes with subsequent oxidative stress and inflammation can lead to fibrosis, which may

ultimately progress to cirrhosis or promote the development of HCC. At the present time, it is regrettable there is no one ideal therapy suitable for all patients. Future trials are required that may combine therapies in an effort to maximize histological benefit, while minimizing side effect profile. For the large number of patients currently affected with this chronic liver disease, clinical trials or a multidisciplinary approach optimizing treatment and metabolic status appear to provide the best available alternatives.

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