NASH: The Hepatic Injury of Metabolic Syndrome: a Brief Update

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Abstract: Non alcoholic fatty liver disease occurs in those who don't consume alcohol in amounts considered harmful to the liver. It represents a spectrum of conditions characterized histologically by mainly macrovesicular hepatic steatosis. There are two histological patterns of NAFLD: fatty liver alone and steatohepatitis. In this brief review, clinical and histologic spectrum, natural history, diagnosis, and management of this condition are discussed.

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Introduction

The association of macro vesicular steatosis of the liver with inflammatory changes and fibrosis in obese subjects has been described for several decades. It was only after few reports documented the development of liver failure in some patients following surgical jejunoileal bypass for morbid obesity that this condition was clinically recognized .In 1980 Ludwig et al introduced the term Non alcoholic steato-hepatitis (NASH) to describe the histological features similar to alcoholic hepatitis (Mallory bodies, ballooning degeneration, hepatocyte necrosis and fibrosis) in non-alcoholic's. [1]

Histologic Criteria for the Diagnosis of NASH

The principal histological feature is the presence of macrovesicular fatty change in hepatocytes with displacement of the nucleus to the edge of the cell Additional presence of Mallory bodies, ballooning degeneration, lobular neutrophilic inflammation and zone 3 perisinusoidal fibrosis. Frequency of Mallory bodies is, however, less frequently in NASH compared with alcoholic hepatitis. [2, 3]

Clinical Spectrum of NAFLD

The spectrum of this condition ranges from clinically silent entity of fatty liver to chronic liver disease with its sequlae.

Epidemiology of NAFLD

Nonalcoholic fatty liver disease (NAFLD) is present in up to one third of the general population and in the majority of patients with metabolic risk factors such as obesity and diabetes. Insulin resistance is a key pathogenic factor resulting in hepatic fat accumulation. Recent evidence demonstrates NAFLD in turn, exacerbates hepatic insulin resistance and often precedes glucose intolerance. Once hepatic steatosis is established, other factors including oxidative stress, mitochondrial dysfunction, gut-derived lipopolysaccharide and adipocytokines, may promote hepatocellular damage, inflammation and progressive liver disease. The causative factors are tabulated in Table (1 and 2). It may be implied that the major key factor causing NASH is central obesity and derangement in lipid metabolism.

Table (1). Laboratory abnormalities.

Pre cirrhosis	Cirrhosis
Hemogram = normal	Hypersplenism features. PT increased, thrombocytopenia,
Liver function tests = 1-4 times elevation of ALT, AST:ALT higher than AST , ALP >2 TIMES	AST levels higher than ALT Serum Albumin reduced before Bilirubin rises
30-50% patients have Diabetes or Glucose intolerance, 20-80% Hyper triglyceridemia	

Table (2). Conditions Associated With Steatohepatitis.

1. Insulin resistance	3. Total parenteral nutrition
a. Syndrome X	4. Severe weight loss
i. Obesity	a. Jejunoileal bypass
ii. Diabetes	b. Gastric bypass
iii. Hypertriglyceridemia	c. Severe starvation
iv. Hypertension	5. Iatrogenic
b. Lipoatrophy	a. Amiodarone
c. Mauriac syndrome	b. Diltiazem
2 Disorders of lipid metabolism	c. Tamoxifen
a. Abetalipoproteinemia	d. Steroids
b. Hypobetalipoproteinemia	e. Highly active antiretroviral therapy
c. Andersen's disease	6. Refeeding syndrome
d. Weber-Christian syndrome	7. Toxic exposure
a. Environmental	
b. Workplace	

Demographics

Earlier reports described NASH to be more common in females but recent studies have shown that this entity is equally common in all age groups including pediatric population and occurs with similar frequency in both the genders. [4, 5] The highest prevalence is in those between 40 and 49 years of age. NASH occurs in families. The causes of such familial clustering include both genetic and environmental factors although clear-cut pattern of inheritance of risk for NAFLD is yet to be unraveled. Various lipid metabolic derangement running in families may be one of the reasons that would explain familial clustering of NASH There is increasing evidence that NAFLD often represents the hepatic component of a "metabolic" syndrome characterized by obesity, hyperinsulinemia, peripheral insulin resistance, diabetes, hypertriglyceridemia, and hypertension. [6,7] Subjects with truncal obesity are more prone to develop NASH, hypertension and diabetes. However, obesity is not invariably present in patients with NASH and many individuals with NASH have normal body weight [8] Type 2 diabetes mellitus is a major component of the metabolic syndrome and is associate with peripheral insulin resistance and hypertriglyceridemia .Diabetes per se predisposes to progressive liver fibrosis. [9]

Fatty Liver to NASH

Fatty liver with inflammatory changes in hepatocytes leads to development of NASH. The presence of peripheral insulin resistance , increased free fatty acids ,and increased hepatic lipid peroxidation have been identified in patients with NASH [10] Further NASH is associated with specific mitochondrial abnormalities with intra-mitochondrial paracrystalline inclusions. [11] It is quite possible that cellular respiratory chain is getting affected in NASH and progressive liver cell damage follows. Iron over load was first reported by Bacon et al [12] in patients with NASH (in 18 of 31). The presence of iron overload has been reported to be associated with increased hepatic fibrosis. [13] However, these data have been refuted in 2 other series. [14, 15]

Symptoms, Signs and laboratory abnormalities*:* NASH is discovered incidentally as most of the patients are asymptomatic. Symptoms and signs are tabulated in Box 1 and 2. Laboratory parameters are essentially nonspecific. Most of the patients have ALT rise in liver function tests and bilirubin levels don't rise till the disease gets advanced Table (2). Later all features of hypersplenism and cirrhosis are reflected in liver function tests.

Box (1). NASH symptoms.

Asymptomatic: majority Fatigue , right hypochondriac pain, Occasional: pruritis , anorexia and nausea , Jaundice and features of decomposition are late manifestations.

Box (2). Signs of NASH.

1.Obesity =30-100% 2. Hepatomegaly =50% 3. Stigmata of chronic liver disease. Very small % (spider nevi and palmer erythema most common 4.Advanced cases: Jaundice, ascites, Flap ,muscle wasting

Diagnosis of NASH: Powell *et al* [16] originally proposed 3 criteria for the diagnosis of NASH:

A histological picture of steatohepatitis, convincing evidence of minimal or no alcohol consumption (40 g/wk), and absence of serologic evidence of viral hepatitis.

It is generally believed that a fatty liver does not develop with alcohol consumption levels <20 g/day. However, there are no published and universally accepted threshold levels of alcohol intake that separate alcoholic fatty liver disease from NAFLD. It is very difficult to get exact history of Alcohol intake and several surrogate markers of excessive alcohol consumption over a period of time have also been evaluated. These include serum glutamyl transferase levels, mean corpuscular volume, AST levels, AST/ALT ratio, mitochondrial AST levels and de-acylated transferrin levels.The first 4 tests are both widely available and relatively inexpensive. Unfortunately, they lack both sensitivity and specificity, and neither the negative nor positive predictive values are high enough to be clinically useful. The presence hepatitis C genotype 3 is associated with steatosis and we can have combination of hepatitis C and NASH in such patients especially if they have metabolic syndrome features.

Noninvasive Methods of Diagnosis

Elevation of liver enzymes doesn't correlate with liver cell injury in NASH. Ultrasound is the most inexpensive modality

in diagnosis of Fatty liver besides CT scan and MRI can identify patients with fatty liver disease.Sonographic criteria of fatty liver include:-A diffuse hyperechoic echo texture, bright liver compared to kidneys, vascular blurring and deep attenuation. CT scan may primarily not be used for diagnosis of NASH but when used for any other reason shows decreased attenuation by about 1.6 Hounsfield units for every milligram of triglyceride deposition per gram of liver CT scan, the sensitivity and specificity are 54% Using a cut off of 20.5 Hounsfield units 80–100 seconds after intravenous contrast injection, a fatty liver could be diagnosed with 86% sensitivity and 87% specificity 95%, In a direct comparison of CT scan with sonography, sonography was found to be more sensitive in detecting fatty change with a sensitivity of 66-100% which is comparable to CT abdomen and MRI. However, when fatty change is patchy or focal, CT scan and MRI are superior to sonography. [17] There is considerable intra individual variation in the diagnosis of fatty liver by these modalities and none of these modalities can distinguish between fatty liver versus steatohepatitis. To quantify fibrosis in NASH fibrosis score was developed based on six variables, a complex system with negative predictive value of 88% in advanced fibrosis. Fibro scan is another non invasive modality, however, performs poorly in obese patients who frequently have NASH. New data with MR Elastography, shows higher sensitivity approaching 98%and specificity of 100%. [18] There are exciting recent data that serum CK-18 fragment, a marker of apoptosis activity is a sensitive and specific marker for NASH This marker together with MR Elastography may negate the need for liver biopsy in most of the patients with NASH. [19]

Indications for Liver Biopsy

Liver biopsy is not routinely indicated in the diagnosis of NASH as the procedure is associated with risks and no definite therapy is available. Further the condition is benign in most of cases so the patients aren't subjected routinely to liver biopsy, however, biopsy may be done to exclude alternate causes of liver disease, ascertainment of degree of fibrosis, and determination of long-term

Prognosis

Natural History of NASH

Fatty infiltration is toxic to hepatocytes and fatty liver causes mitochondrial injury and progresses to NASH and may result in steatohepatitis with fibrosis and eventually cirrohosis .The exact duration of progression has been varied in different studies with one study showing no progression of fatty liver to NASH in a ten year follow-up. [5] About 30-40% NASH have advanced fibrosis where as 10-15% have established cirrhosis (20.21). At presentation. Histological improvement has been documented in patients with minimal fibrosis with slow weight reduction as rapid weight loss is known to accelerate progression of the disease.

Although most patients with NASH without bridging fibrosis or cirrhosis have a very low risk of death up to 5–10 years from the time of diagnosis, those with more advanced disease are at higher risk of dying as a consequence of their NASH.

Treatment of Risk Factors

A) Weight management: In overweight individuals with elevated aminotransferase levels, weight reduction by 10% or more has been shown to correct aminotransferase activities and decrease hepatomegaly. [22] Weight reduction,however,should be gradual.

B) Exercise: The value of exercise in achieving and maintenance of weight loss is now well established. [23-25] Exercise has been shown to increase the oxidative capacity of muscle cells and utilization of fatty acids for oxidation This decreases fatty acid and triglyceride accumulation in the myocytes and thereby improves insulin sensitivity The degree of improvement in insulin sensitivity is related to the intensity of the exercise

Pharmacologic Treatment of Insulin Resistance

Insulin resistance is the common denominator of NASH and factors causing increased fatty acid delivery to liver lead to hepatocytic dysfunction. Studies with various pharmacological agents like Metformin, Rosiglitazone, Vitamin E UDCA, clofibrate, Taurine, have shown to decrease liver enzyme levels but either the effects get reversed after stoppage of the drug or the toxicity precludes their use.

Vitamin E and C: A placebo-controlled trial involving 45 patients concluded that six months of treatment with a combination of vitamin E and C (1000 IU and 1000 mg, respectively) was associated with significant improvement in liver fibrosis [26]

Metformin: Aminotransferase normalization was more likely with metformin than with weight loss and vitamin E in a randomized trial. [27]

Pioglitazone: Several studies have shown biochemical and histologic improvement with pioglitazone but the improvements appear to reverse upon discontinuation.

Rosiglitazone: — a controlled trial showed the patients randomized to rosiglitazone had improvement significantly in steatosis and normalized aminotransferase levels. [28]

Ursodeoxycholic acid: a large controlled trial showed no benefit

Orlistat*:* A gastrointestinal lipase inhibitor, a pilot randomized controlled trial in patients with NASH found a significant reduction in fatty liver as assessed by ultrasound. [29]

NASH can progress to cirrhosis especially when on histological features of bridging fibrosis are present. Older subjects and diabetics are at greater risk. No definite therapy is yet available to reverse this pathological process Treatment of the underlying condition, meticulous control of diabetes and correction of dyslipidemia are imperative.

Conclusion:

NASH is the hepatic injury of the metabolic syndrome and constitutes a very important cause of cryptogenic cirrhosis. There is no definite treatment. Management is to focus the optimal weight and regular exercise besides correction of dyslipidemia and meticulous control of underlying diabetes.

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