

NASH:

The Next Big Liver Disease

"....this (NASH) is going to be the next big liver disease after hepatitis C in this country.... we now estimate that at least three percent of the entire U.S. population, in fact, has steatohepatitis...NASH is going to be an even bigger epidemic as we grow more sedentary and more obese." IRONUSA 2000 Herbert Bonkovsky, MD
Iron Disorders Institute, Scientific Advisory Board Chair

Nonalcoholic steatohepatitis (NASH) was first described in 1980 by Dr. Ludwig, of Mayo Clinic, who observed a condition that was similar to alcoholic hepatitis, but in patients who did not consume alcohol. The condition is defined by the presence of steatosis (fatty deposits) and hepatitis (inflammation of the liver) in the absence of alcoholism.

NASH is a class of non-alcoholic fatty liver disease and has also been called diabetic hepatitis, fatty-liver hepatitis, alcohol-like hepatitis, or pseudo-alcoholic hepatitis. NASH is mostly seen in patients between the ages of 40 and 60 years, although the condition can also occur in children.

Previously, NASH was diagnosed more often in women than in men, possibly because women seek medical attention more readily than do men. Presently, experts find that NASH is actually as prevalent, in men as in women. Some have commented that men with this disorder are meat eaters and that they especially consume red meats that are high in fat.

Typically, NASH is a chronic condition, persisting for many years. Fortunately, it is usually not rapidly progressive or severe, although patients with NASH can develop cirrhosis. A progression to cirrhosis occurs in as many as 26% of patients with NASH, whereas nearly half of the patients with alcohol-related hepatitis will progress to cirrhosis.

Patients who have cirrhosis are at risk for various complications including mental problems such as confusion or memory loss (hepatic encephalopathy), bleeding into the gastrointestinal tract resulting in anemia, fluid accumulation in the abdomen (ascites) or in the lower extremities (edema), or liver cancer. Even though patients with cirrhosis due to NASH may ultimately require liver transplantation to survive, often they are not candidates because of obesity, complications of diabetes, or other reasons.

Symptoms, findings and clinical features: Many people with NASH have no symptoms and may seek medical attention because of fatigue. Often elevated liver enzymes prompt a referral to a gastroenterologist or hepatologist. Primary NASH is most frequently associated with obesity, and insulin resistant diabetes (type II diabetes mellitus) whereas secondary NASH is related to other factors, such as medications: synthetic estrogen, some breast cancer drugs (tamoxifen), glucocorticoids, amiodarone, or perhexilene-maleate. Exposure to industrial solvents, other diseases such as Celiac or Wilson's, surgical procedures for treatment of obesity such as jejunal bypass, small bowel

resection, bacterial overgrowth and rapid weight loss are among the other miscellaneous factors that result in NASH.

The cause of NASH is not fully known, probably because the pathogenesis (the origin and development of disease) is multi-factorial. A combination of genetics, hyperinsulinemia, decreased synthesis or secretion of the good fats (high density lipoproteins), increased levels of bad fats (saturated fatty acids) and oxidation of these bad fats might be key to development of NASH. Iron might also be playing a contributory role, because iron is a known catalyst for free radical production resulting in oxidative stress. Elevated levels of serum ferritin, which is an indicator of storage iron and positive liver iron stains are often observed in patients with NASH. Further, NASH patients who are homozygous for the C282Y major mutation of *HFE*, the gene effected in classical hereditary hemochromatosis, can exhibit significantly higher ALT levels and more hepatic fibrosis than those without the mutations of *HFE*.

Proper diagnosis of NASH is dependent being able to exclude alcohol abuse. Also, experts are still not fully in agreement about how much alcohol is excessive. Indeed, in many persons, small amounts of alcohol may be beneficial by increasing levels of good (HDL) cholesterol. Presently, two servings of wine per day or its equivalent in other forms of alcohol is the agreed upon acceptable level of alcohol consumption for normal adult men and one to one to one and half servings for adult women.

Determining whether a patient is a mild, moderate or excessive drinker is sometimes a challenge for the physician. Talking to the spouse or to a significant other and getting independent confirmation is generally the best approach.

It is difficult to differentiate NASH from alcoholic hepatitis based solely on clinical evaluation, although there are a few useful indicators that can help rule out excessive alcohol consumption. According to Dr. H.S. Ballard, associate chief of hematology and oncology at the New York Department of Veterans Affairs Medical Center, New York, New York "The presence of carbohydrate-deficient transferrin (CDT) in the blood and an increase in the size of red blood cells (macrocytosis), as measured by the mean corpuscular volume (MCV) are often seen in alcoholics."

Carbohydrate-Deficient Transferrin (CDT): Transferrin is an iron-containing protein in the plasma that transports iron, which is stored at various sites in the body, to the developing red blood cells (RBC's) in the bone marrow for incorporation into hemoglobin. Transferrin molecules in the blood usually contain several carbohydrate components. In chronic heavy drinkers, however, the number of carbohydrate components in each transferrin

molecule is reduced, resulting in CDT. The mechanisms underlying this alteration still are unclear.

Moderately increased MCV may be a clue to unsuspected alcoholism. Analysis of blood smears can support this diagnosis. In patients with an alcohol-related increase in MCV, the enlarged RBC's are round and of uniform size. Conversely, in patients with certain types of anemia that result in an increased MCV, the RBC's typically are oval and of variable size.

Liver tests can be helpful for diagnosing NASH and for differentiating NASH from alcoholic hepatitis. Two liver enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in about 90 percent of people with NASH. In many liver diseases, such as NASH or viral hepatitis, the ratio of AST to ALT is usually less than one. In contrast, in patients with alcoholic liver disease this ratio is greater than one. Ratios of 2 or higher virtually always point to excess alcohol use.

In a British study of 85 patients, (40 non alcoholics) AST/ALT ratio and mAST (mitochondrial AST) correctly classified 87.9% of cases into either the alcoholic or NALD groups. Among the alcoholics the AST/ALT ratio was higher, where patients with NAFLD had higher levels of ALT.

Imaging tests, such as ultrasound, computed tomography (CAT-scan), or magnetic resonance imaging (MRI) can reveal fat accumulation in the liver when the fat content is greater than 25%. MRI cannot detect fibrosis or inflammation. MRI can detect excessive hepatic iron; the iron overloaded liver appears "black" on MRI.

According to Dr. Jacqueline Laurin, University of Maryland, Baltimore in addition to liver biopsy, "Valuable blood tests include hepatitis B and C serology, iron profile (serum iron, iron binding capacity and serum ferritin), alpha 1-antitrypsin phenotype, ceruloplasmin, antinuclear antibody and antismooth muscle antibody, and serum protein electrophoresis." Other helpful tests are platelet and complete blood count. Laurin adds that "If these tests are negative or normal, and if there are no symptoms or signs of chronic liver disease, it is unlikely that a specifically treatable liver disease would be discovered at biopsy." Nevertheless, liver biopsy retains its value in showing best the severity (stage) of liver disease and aids in estimating prognosis.

Treatment and Cure:

There is no cure for NASH. The present treatment for NASH consists of managing the various conditions associated with the disease, such as obesity, diabetes, and hyperlipidemia

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NASH continued

"Exercise and diet continue to be the cornerstone of therapy."

Neuschwander-Tetri BA and Caldwell SH. 2002 Summary of AASLD Conference on Nonalcoholic Steatohepatitis (NASH) *Hepatology* 37 (2003): 1202-19.

and monitoring patients for progression to cirrhosis. The cornerstone of management is weight reduction in the overweight or obese patients. Reducing body weight by 10-15% can improve ALT and AST levels. Weight loss should be slow, no more than one to two pounds a week. Rapid weight loss can contribute to oxidative stress, which increases the patient's risk for progression to cirrhosis.

Gastric or jejunoileal bypass are surgical procedures that are no longer considered for NASH patients due to complications such as overwhelming bacterial infections, malnutrition and liver failure. In 1999, the FDA approved adjustable gastric banding as a weight reduction procedure, which appears to be safer. One of the benefits of this procedure is that it allows for a more gradual loss of weight (6-10 pounds month). Gastric banding and bypass procedures have been associated with improvements in NAFL/NASH although the number of subjects studied and the duration of follow-up are limited.

Oral anti-diabetic drugs have been used in the treatment of NASH patients. These drugs have been effective in improving insulin sensitivity, but the long-term benefit to the liver from this type of medication remains undetermined.

Lipid lowering drugs such as the statins (atorvastatin, pravastatin or simvastatin), may also be effective. In a small pilot study of seven patients with NASH who were given atorvastatin for one year, findings including liver biopsy revealed improvement in lipid levels and inflammation. Another larger study, which included comparison of various statin drugs, found that atorvastatin and simvastatin were the most effective. However, statin drugs may lead to mitochondrial injury or muscle damage.

Ursodeoxycholic Acid (UDCA) is a bile acid. Synthetic UDCA is marketed in the US as brand name Actigall; the generic form is called ursodiol. Previously, investigators found that people with NASH who were treated with UDCA for one year had improved liver function tests and decreased fat accumulation in the liver. However, a more recent large multi-center Urso250 trial showed that UDCA is of no benefit in NASH.

Although, many drugs have been suggested and tested in small trials, none has been shown to be a long-term benefit, and none yet is FDA-approved for therapy of NASH.

Alternative medicines:

Silymarin, the main active ingredient of milk thistle and many other herbal remedies have been claimed to be of benefit in liver disease. However, good quality evidence of benefit in

properly done clinical trials is meager or non-existent. Indeed, some so-called herbal remedies (germander, pennyroyal) are toxic to the liver. Then, too, such concoctions are not subject to FDA oversight or regulation, and their actual compositions are often different from what is claimed.

Antioxidants such as vitamin C or E have been used by some clinicians in the treatment of NASH, however the benefit to the patient is not fully known. A few small studies suggest that vitamin E may be of benefit, particularly for children with NASH.

Iron reduction by therapeutic phlebotomy may be helpful for patients with NASH. Elevations in serum ferritin occur frequently in NASH, and stainable iron is often detected in the livers of patients with NASH. Excess iron is known to accelerate cell death by contributing to increased oxidative stress and free radical activity. Ideally, the serum ferritin level should be lowered to 20ng/mL on one occasion and thereafter, periodic phlebotomy should continue to keep serum ferritin levels within a recommended range of 25-75ng/mL. Such iron reduction therapy has led to improvement in measure of liver inflammation (serum ALT) and in insulin sensitivity.

Prognosis:

More studies are needed to better understand the course of NASH. Usually the short-term prognosis is relatively good. The five-year survival probability for patients with alcoholic hepatitis is less than 40%; for patients with NASH it is nearly 70%. The ten-year survival probability of alcoholic hepatitis drops dramatically to 15%, for NASH the ten-year survival probability is nearly 60%.

Future:

At The American Association for the Study of Liver Diseases (AASLD) Conference on Non-alcoholic Steatohepatitis (NASH) Atlanta, Georgia, September 2002, many concerns were expressed. A summary of the presentations and discussion provides an organized plan for studying fatty liver diseases. According to the AASLD summary, there is much need for more concise methods for diagnosis, alcohol consumption guidelines, the need for research on possible therapies, including the use of certain anti-diabetes, lipid reduction medications and alternative medicines as well as the need for research.

As of June 1, 2003, the Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) created the Liver Disease Research Branch within the Division of Digestive Diseases and Nutrition and appointed

Dr. Jay Hoofnagle as its founding director. The Branch will also include Dr. Leonard Seeff, special expert on viral hepatitis, and Dr. Jose Serrano, Director for the Liver and Biliary Disease Program.

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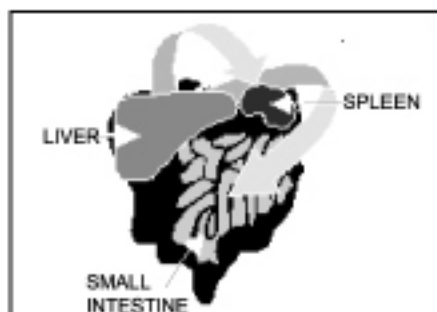
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Continued from cover: Hepcidin

The second action then causes an increase in ferritin synthesis within the macrophages. Because hepcidin is a small peptide molecule, it is excreted into urine by the kidneys.

Nevertheless, as long as the invasion emergency persists, the patient's hepatocytes continue to form more hepcidin under the influence of interleukin-6. Remarkably, hepcidin synthesis is increased not only in response to invasion but also to iron over-loading and, production of the hormone is decreased in iron deficiency. Unfortunately however, in humans and in mice with hemochromatosis (HHC), hepcidin synthesis is severely depressed (1,2). Thus in HHC, not only is excessive iron absorbed in the duodenum but also macrophages fail to retain the surplus metal.

Furthermore, persons who are heterozygote carriers of both an *HFE* gene mutation and a hepcidin gene mutation may have an increase in clinical problems (4). Accordingly, there is considerable hope that the hepcidin hormone might be developed into a useful drug to assist persons who have HHC gene mutations to adjust their iron metabolism into normal ranges.(6)



HOW HEPCIDIN WORKS

- It is made in the liver
- It is increased by inflammation, or when iron stores are sufficient
- It inhibits iron uptake by the small intestine
- It inhibits recycled iron release from macrophages, many in the spleen.

Image Content Courtesy of Thomas Ganz, Ph.D.

HEPCIDIN

Condition	Hepcidin Synthesis	Action	Effect on Serum Iron
Microbial or cancer cell invasion	↑	Macrophage iron release blocked	↓
Non- <i>HFE</i> related iron loading	↑	Duodenal iron absorption blocked	↓
Iron deficiency Low red blood cells	↓	Duodenal iron absorption permitted Macrophage iron release permitted	↑

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Diet Recommendations for Patients with NASH:

Weight reduction recommendations for patients with NASH include regular exercise and avoiding or limiting consumption of certain foods. Sugar and refined flours or foods high in starch influence blood sugar levels and contribute to body fat. Among the culprits are white table sugar, and white bread, pasta, rice, potatoes and corn. Sugary cereals should also be avoided.

For patients with any degree of liver damage, consumption of tannins which are contained in coffee, tea and red wines should be limited.

Some NASH patients with cirrhosis may develop a severe condition called hepatic encephalopathy (HE). HE is a condition that can occur in patients with cirrhosis of the liver possibly as a result of high ammonia levels. HE is characterized by personality changes, intellectual impairment, and unconsciousness. It is estimated that signs of hepatic encephalopathy can be observed in as many as 70% of patients with cirrhosis. The patient featured in the article "In Their Own Words" Vester Cox, was hospitalized for hepatic

DIET PLAN for Patients with NASH

INCLUDE	LIMIT	LIMIT
Use of refined sugar, flour and foods that are high in starch	White sugar, white bread including bagels, pasta, rice, potato, corn	
Use of tannins: coffee, tea and red wine	Especially if cirrhosis is present	
Daily calories to 2,000	Balance daily menu to include servings of all food groups: 2 dairy, 6 meat, 5 whole grains (bread, cereal) 4 veggies, 3 fruits, 4 fats, 1 dessert	
Daily exercise	Unless otherwise advised by your physician, 20 minutes daily exercise such as walking, swimming, dancing, gardening....	

encephalopathy. Vester was given additional diet restrictions that limited sodium (including salt substitutes) and consumption of any ammonia producing food such as onions, Jello, jelly beans, cheese, deli meats, frozen fish, nuts and red beans.

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Resources:

National Institute of Diabetes and Digestive and Kidney Diseases (<http://www.niddk.nih.gov>)

The American Association for the Study of Liver Diseases <http://www.aasld.org>

The American Liver Foundation <http://www.liverfoundation.org>

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