The Liver-Biliary-Pancreatic Center Newsletter

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Dear Colleagues,

Obesity and its manifold attendant ills are epidemic in the United States and other developed countries. This epidemic has been the subject of numerous recent publications and other communications from the Centers for Disease Control, the National Institutes of Health and other governmental agencies. Among the major complications and attendant abnormalities are the metabolic syndrome with systemic arterial hypertension, hypercholesterolemia, hypertriglyceridemia, insulin resistance and hyperuricemia. *The major hepatic manifestation of obesity, the metabolic syndrome, diabetes mellitus and insulin resistance is non-alcoholic fatty liver disease (NAFLD).* This edition's feature article by Steven Zacks, MD, provides an overview of NAFLD. Although usually benign, the more serious form of this disorder – non-alcoholic steatohepatitis (NASH) – carries with it a clear risk of advanced fibrosis, cirrhosis, decompensated liver disease and hepatocellular carcinoma.

The treatment of choice for NAFLD is gradual weight loss accompanied by other lifestyle changes including increased exercise, and the avoidance of smoking, drinking excess alcohol and other unhealthy behaviors. Bariatric surgery has also been shown to be highly-effective, and we are fortunate at Carolinas Medical Center to have an active, multidisciplinary weight management and wellness center – Carolinas Weight Management and Wellness Center directed by Drs. John Cleek and Keith Gersin. The medical teams of the Liver-Biliary-Pancreatic Center and Carolinas Weight Management and Wellness Center look forward to helping you and your patients with obesity, metabolic syndrome, fatty liver and other liver disorders.

Yours truly,

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Non-alcoholic Fatty Liver Disease: An Epidemic of Affluent Societies

By Steven Zacks, MD

Definition and Epidemiology

Non-alcoholic fatty liver disease (NAFLD), the preferred term linking insulin resistance to hepatic involvement, is a spectrum of disease. The earliest recognizable stage is steatosis, or fat accumulation in the liver without inflammation. Simple steatosis is considered relatively benign. The next stage, non-alcoholic steatohepatitis (NASH), is characterized by steatosis with hepatocellular injury and inflammation either with or without fibrosis. Patients with NASH are at a much higher risk of progression to cirrhosis. In the absence of overt cirrhosis, differentiation between these stages is only possible by histological examination of a liver biopsy.

Liver steatosis is the most frequently diagnosed chronic liver disease.[1] The estimated prevalence of NAFLD in the general population of western countries is 20–40 percent. Prevalence is higher among the obese and diabetic population.[2,3] Non-alcoholic steatohepatitis accounts for about 20 percent of NAFLD, so the estimated prevalence of NASH in western countries is two–three percent, and probably is the cause of about 80 percent of cryptogenic cirrhosis.[4] Patient characteristics vary according to region and race. In the United States, NAFLD is three to five times more common in men than in women, and is also more prevalent among Hispanics than among whites and blacks.[5]

Differentiation between simple fatty liver and NASH is important. Currently, this is possible only by histological examination of a liver biopsy.

The prevalence of NAFLD increases in parallel with weight or body mass index (BMI). The prevalence of steatosis in obese individuals (BMI>30 kg/m^2) and morbidly obese individuals (BMI>35 kg/m^2) is estimated at 65–75 percent [6,7] and 85–90 percent, [6,8] respectively. In obese individuals, the prevalence of NASH increases disproportionately. Studies suggest that as many as 15–20 percent of obese individuals have NASH. Similarly, the vast majority of individuals with NAFLD are either overweight or obese.[9] Studies of NASH patients suggest that between 40 and 95 percent will be obese, more than half may have Type 2 diabetes mellitus and up to 80 percent may have dyslipidemia. [10]

Differential Diagnosis

The major risk factors for the accumulation of excess liver fat in NAFLD are obesity and insulin resistance. Secondary fatty liver disease, as opposed to primary fatty liver disease or NAFLD, can be due to disorders of lipid metabolism, refeeding syndrome, severe weight loss following jejunoileal or gastric bypass, lipodystrophy, total parenteral nutrition, toxic exposure to organic solvent, or medications such as amiodarone, diltiazem, corticosteroids, synthetic estrogens, tamoxifen and highly active antiretroviral therapy for HIV. Clinicians should exclude most of the potential causes for secondary fatty liver during history taking, although a degree of overlap between NAFLD and fatty liver secondary to alcohol excess probably occurs in some individuals. By convention, the diagnosis of non-alcoholic fatty liver disease requires that daily alcohol intake be less than 20 g per day for women and less than 30 g per day for men. This equates to no more than two standard alcoholic drinks per day for men and one and a half standard alcoholic drinks per day for women. A standard drink contains 14 g of alcohol (12 ounces of beer, five ounces of wine, or one and a half ounces of spirits).[11]

Persons with diabetes mellitus are at higher relative risk of death from liver cirrhosis (odds ratio 4.3) than from ischemic heart disease (odds ratio 1.8).

Risk Factors for NAFLD

Frequent association with glucose and lipid metabolism disturbances often renders NAFLD a "satellite" element of metabolic syndrome.[12,13] The prevalence of metabolic syndrome in patients with NAFLD is more than 40 percent. Metabolic syndrome is a strong predictor of NAFLD, particularly among those of Japanese descent.[14] Factors linked with severity of disease include being over 50 years of age, having a body mass index greater than 30, and having a chronic elevation of serum aminotransferase levels (ALT, AST) to twice the normal range.[4] Diabetes and obesity are risk factors for progression to hepatic fibrosis.[15,16] Diabetes is also a risk factor for death among patients with NAFLD.[17]

Pathogenesis

In NAFLD, fatty infiltration is classified as mild if fat involves less than 30 percent of hepatocytes, moderate if it involves up to 60 percent and severe if it involves greater than 60 percent.[18] Accumulation of triglycerides in hepatocytes can regress once the cause is eliminated. Non-alcoholic fatty liver disease arises mainly from insulin resistance, abnormal secretion of some hormones governing glucose and lipid metabolism (leptin, adiponectin), and increased release of inflammatory cytokines (tumor necrosis factor-a, interleukins).[19,20]

Persons with diabetes mellitus are at higher relative risk of death from liver cirrhosis (odds ratio 4.3) than from ischemic heart disease (odds ratio 1.8).

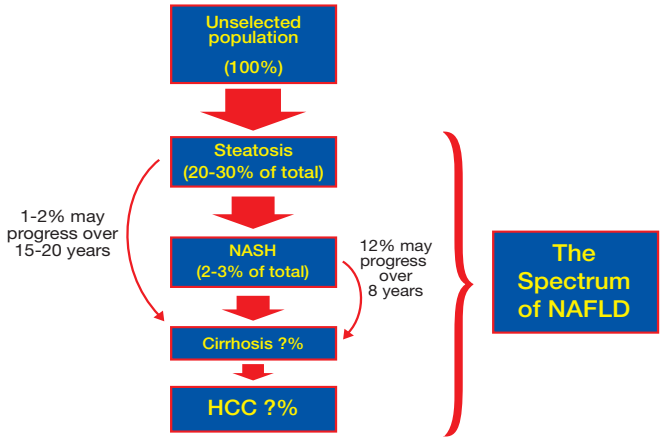
Increased flow of free fatty acids from visceral fat to the liver via

the portal vein further contributes to impaired intracellular lipid metabolism.[21,22] In hepatocytes, both insulin resistance and excess free fatty acids impair mitochondrial oxidation of fatty acids, which accumulate and contribute to generation of free radicals by activating the metabolic pathways of peroxisomes and microsomes leading to the hepatitis.[23] Other factors that increase oxidative stress, such as iron, drugs, alcohol, toxins and genetic factors, play variable co-morbid roles.

Natural History

NASH is a risk factor for increased mortality, and about one in eight patients with NASH develop cirrhosis during the ensuing eight to 10 years (Figure 1). Data on long-term outcomes of NASH-associated cirrhosis suggest that liver failure is the main cause of morbidity and mortality.[24] The likelihood that someone with NAFLD will develop progressive liver dysfunction over 15 to 20 years is one–two percent.[25] Risk of hepatocellular carcinoma is doubled among diabetic men with NAFLD.26 Persons with diabetes mellitus are at higher relative risk of death from liver cirrhosis (odds ratio, 4.3) than from ischemic heart disease (odds ratio, 1.8).[27]

Figure 1: Prevalence and Outcomes of Non-alcoholic fatty liver disease [NAFLD]



Abbreviations: HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Adapted with permission from Preiss D, Sattar N. Non-alcoholic Fatty Liver Disease: An Overview of Prevalence, Diagnosis, Pathogenesis and Treatment Considerations. Clinical Science 2008; 115(5):141–150.

Clinical Findings

Most individuals with NAFLD are asymptomatic. The diagnosis often follows abnormal findings of liver chemistries prior to starting medication, abnormal findings of abdominal ultrasounds performed for another reason, or abnormal findings during the assessment of cardiovascular risk of the investigation of metabolic syndrome features. If advanced cirrhosis develops prior to diagnosis, presentation is similar to cirrhosis due to other causes. Clinical signs, including ascites, splenomegaly, encephalopathy and variceal bleeding may occur. Indeed, NAFLD is now recognized as the most common cause of cryptogenic cirrhosis (~80 percent) [4] and has been estimated to be the underlying diagnosis in 10 percent of liver transplant candidates.

The overweight or obese patient with abnormal liver enzyme tests, with raised or high–normal fasting blood glucose, low HDL-cholesterol and elevated fasting triglycerides is likely to have NAFLD. Typically, fatty liver is associated with elevated serum ALT and GGT. However, neither is sufficiently sensitive nor specific for the diagnosis of NAFLD. ALT and GGT are of most clinical use when combined with clinical findings.

Treatment

No general consensus exists on the effectiveness of any therapeutic agent for treating NAFLD. Treatment strategies for NAFLD include identification and treatment of associated metabolic disturbances, including lifestyle modifications to reduce the likelihood that patients will develop metabolic syndrome (Table 1). If a patient is obese, he or she should be encouraged to start with regular and gradually increasing aerobic activity. Dietary restriction of about 25–30 kcal/kg daily is reasonable, with a target weight loss of about 10 percent of body weight over six months.[28] Although many medications have had promising results in preliminary pilot studies, few treatments have been examined in randomized, controlled trials.

Table 1: Therapeutic Approaches to Patients with NAFLD

Lifestyle, Diet and Weight Reduction
• Caloric restriction
• More physical activity
• Bariatric surgery
Insulin Sensitizers
• Metformin
• Thiazolidinediones
Reduction of Oxidative Stress
• Vitamin E (tocopherols)
• Iron reduction, especially in those with elevated serum ferritin

Bariatric surgery, through weight loss and improvement in the metabolic syndrome, can improve NAFLD. In one study, NASH resolved in 82 percent of patients undergoing laparoscopic adjustable gastric banding after mean weight loss of 34 ± 17 kg. Patients who had metabolic syndrome showed a greater improvement in liver histology with weight loss.[29] In a recent clinical trial, patients with biopsy-proven NASH were randomized to a regimen containing pioglitazone 45 mg daily and hypocaloric diet vs. hypocaloric diet alone for six months. This study showed biochemical and histological improvement associated with the pioglitazone arm.[30] Despite this encouraging data, important drawbacks of these agents are weight gain, osteoporosis, possible increased cardiovascular risks and the temporary nature of the improvements, which imply the need for protracted, perhaps, life-

NAFLD is now recognized as the most common cause (~80 percent) of cryptogenic cirrhosis and is thought to be the underlying diagnosis in ~10 percent of liver transplant candidates.

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long therapy. Several small clinical trials have reported the potential efficacy of metformin in treating NASH.[31,32] Although metformin was well-tolerated and biochemical improvement was shown, histological data remain very limited. In summary, there is no established FDA-approved medication for treatment of NASH. Therefore, there is ongoing and urgent need for prospective, randomized, controlled clinical trials of additional therapeutic approaches to management. We at CMC are involved actively in such trials. For more information, review the summary listing of active clinical trials in this newsletter or contact our clinical research coordinators Gale Groseclose, RN, at 704-355-4875 or Reggie McFadden, RN, at 704-355-7608.

Fatty liver is epidemic in the United States. The prevalence in adults is 20-40 percent. The prevalence of NASH is two–three percent, but among the obese, it is 15–20 percent.

Summary

NAFLD is among the most common causes of chronic liver disease worldwide, and can potentially progress to cirrhosis, liver failure and hepatocellular carcinoma. Investigations over the last two decades have led to a better understanding of the natural history, epidemiology and pathophysiology of this disease. However, despite having tested a large number of agents, no single agent or combination of agents has emerged as a therapy with proven efficacy. A multidisciplinary approach, emphasizing weight loss, exercise, healthy diets and optimizing metabolic risk factors is currently the best option. It remains to be seen whether the results of ongoing randomized, double-blind, placebo-controlled trials to investigate multiple therapeutic options will lead to safe, effective and economical therapeutic alternatives.

In summary, there is no established FDA-approved medication for treatment of NASH. Therefore, there is ongoing and urgent need for prospective, randomized, controlled clinical trials of additional therapeutic approaches to management.

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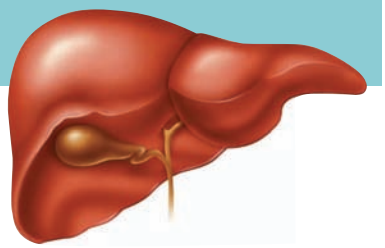
Welcome
Tarun Narang, MD

Tarun completed his residency training in New York at Lincoln Medical Center and began a 1 year fellowship in Hepatology and Liver Transplantation at CMC in July 2009. His clinical interests include viral hepatitis, portal hypertension and cirrhosis. He is also involved in research on Drug Induced Liver Injury and Colorectal Cancer.

Active Clinical Studies at our LBP Center



Trial Name: Drug-Induced Liver Injury Network

A multi-center, longitudinal study of drug- and CAM-induced liver injury

Who May Be Eligible

Patients with evidence of liver injury that is known or suspected to be related to consumption of a drug or Complementary-Alternative Medicine (CAM) within the past six months.

Principal Investigators

Herbert Bonkovsky, MD
Mark Russo, MD

Trial Name: InVision Image Guidance

Advanced image guidance system for open tumor ablation: a pilot study to evaluate accuracy of probe placement

Who May Be Eligible

Male and female adult patients who present with hepatocellular carcinoma, and for whom treatment by means of traditional, ultrasound-guided, microwave ablation during open surgery is appropriate.

Principal Investigators

David Iannitti, MD
John Martinie, MD

Trial Name: TheraSphere®

A humanitarian device exemption use protocol of TheraSphere® for treatment of unresectable hepatocellular carcinoma.

Who May Be Eligible

Patients with hepatocellular carcinoma of the liver who are not surgical resection candidates.

Principal Investigator

David Iannitti, MD

Trial Name: GIDEON

An International Non-Interventional Study with sorafenib (Nexavar®) to evaluate the safety in patients with unresectable hepatocellular carcinoma (HCC) who are being treated with sorafenib

Who May Be Eligible

Patients with unresectable HCC who are candidates for systemic therapy and in whom a decision to treat with sorafenib has been made.

Principal Investigator

David Iannitti, MD

Trial Name: MK7009-009, an HCV protease inhibitor

Phase II study of MK7009 with pegylated interferon and ribavirin for patients with chronic hepatitis C who had a partial or breakthrough response to previous treatment

Who May Be Eligible

Persons 18 years of age or older infected with the HCV genotype 1 who had greater than 2- log10 IU/mL drop in HCV RNA at treatment week 12 but had detectable HCV RNA at treatment week 24 or have detectable HCV RNA during treatment after initially achieving undetectable HCV RNA.

Principal Investigator

Mark Russo, MD

Trial Name: P06086

Phase III study of Boceprevir and PegInterferon/ribavirin for treatment of chronic hepatitis C in treatment naïve subjects with comparison of erythropoietin versus ribavirin dose reduction in the management of anemia.

Who May Be Eligible

Male and female adult subjects who have previously documented chronic hepatitis C genotype 1 infection. No co-infection with HIV or hepatitis B. Hgb at screening must be less than or equal to 15 g/dL.

Principal Investigator

Mark Russo, MD

Upcoming Study

• Phase III study comparing efficacy and safety of TachoSil® versus standard hemostatic fleece material for the secondary treatment of local bleeding in hepatic resection surgery (PI- David Iannitti, MD)

• A Phase III, Multicentre, Double-Blind, Randomised, Placebo-Controlled Study to Confirm the Safety and Efficacy of Subcutaneous Bioresorbable Afamelanotide Implants in Patients with Erythropoietic Protoporphyria (EPP) (PI – Herbert Bonkovsky, MD

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