Update on Current Standards of Care in the Diagnosis and Management of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH): Diagnosis

Part 1

Steatosis (fatty infiltration of the liver) or Non-Alcoholic Fatty Liver Disease (NAFLD) is increasingly recognized as a ubiquitous cause of chronic liver disease. It represents a spectrum of fatty liver without inflammation to steatosis accompanied by inflammation, and fibrosis [NASH]. NAFLD/NASH is associated with obesity, hypertension hyperlipidemia, diabetes mellitus and insulin resistance—disorders collectively known as the Metabolic Syndrome. NAFLD is potentially progressive and may lead to NASH (non-alcoholic steatohepatitis) which is a chronic disease characterized by diffuse fatty infiltration, lobular inflammation, with or without perisinusoidal fibrosis. NASH can lead to cirrhosis and end stage liver disease ultimately requiring liver transplantation. NASH can be silent without any physical symptoms or lab abnormalities and be associated with end stage “cryptogenic” cirrhosis as well as hepatic cancer. For that reason physicians must be more alert in recognizing the clinical features of NASH so that earlier diagnosis, treatment and at least monitoring, can be initiated. Previous published articles

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dealing with the medical treatment of NAFLD/NASH mostly include drug studies that have been open labeled, and not double blind placebo controlled studies. There is still no evidence-based definitive medical treatment of NASH. However there is promising data on some therapeutic measures. This article will objectively review what we know of the recommendations and the standard of care in the medical treatment of NAFLD/NASH.

**HISTOLOGY**

In a thorough technical review of the subject for the American Gastroenterology Association, Sanyal, et al (1) categorized the microvesicular and macrovesicular steatosis as the two major histologic patterns of hepatic steatosis and NAFLD. Lobular hepatitis with necrosis or ballooning degeneration and/or fibrosis is seen. The microscopic features of NAFLD and NASH are indistinguishable from those of alcoholic fatty liver disease.

Based on these findings of steatosis, hepatocyte ballooning degeneration, diffuse lobular acute and chronic inflammation, a perivenular, perisinusoidal collagen deposition, Mallory’s hyaline, vacuolated nuclei in periportal hepatocytes, lobular lipogranulomas, and PAS-diastase resistant Kupffer cells, bridging septa and cirrhosis, a scoring system has been proposed by Brunt, et al (2) to indicate the grade of inflammation and assessment of perisinusoidal fibrosis, portal fibrosis, and bridging.

**EPIDEMIOLOGY**

Ludwig, et al first described NASH(3), as a “hitherto unnamed disease that mimics alcoholic hepatitis histologically, and not related to alcohol consumption.” NAFLD may be the most prevalent form of hepatic disease in the United States (4,5) with a spectrum ranging from relatively benign NAFLD/mild hepatic steatosis to more severe NAFLD/NASH and ultimately to end stage cirrhosis. The prevalence of NAFLD ranges between 15% to 18% (6,7); whereas the prevalence of histology proven NASH in the general population is about 2%–4%(8). In adult patients undergoing liver biopsies, presumably for abnormal liver tests [LFTs], NASH was identified in 7%–9% in Western countries (3,6) and in 1.2% of Japanese patients (9). Zamir, et al (10) reports that more than half of his obese patients in Israel had NAFLD.

The incidence of NAFLD/NASH is very high in morbidly obese patients. Del Gaudio, et al (11) found that obesity is an independent risk factor for liver damage. The majority of cases are between the ages of 40 and 60, although there have been reports in children as young as ten years of age (12,13).

Feldstein and coworkers (14) reported on their experience with 57 children with NAFLD seen at the Mayo Clinic between 1986 and 2000, followed longitudinally up to March 2003. Whereas most adults with NAFLD are asymptomatic many of the children had symptoms related to NAFLD. Abdominal pain was reported in 53% and fatigue in 26% of patients. Physical examination, included hepatomegaly (26%) and acanthosis nigricans (9%). Most patients were obese (72%) and had dyslipidemia (78%).

This problem is often found in adolescence, even in non-Western countries. Nakao, et al (15) diagnosed 105 out of 1,202 university students with NAFLD in Japan. Using multiple measurements the authors determined that visceral fat distribution is a key risk factor for NASH in young adults. Some maintain that NASH progresses to cirrhosis less frequently when compared with alcoholic hepatitis (16–22) but firm evidence is lacking.

**NASH RELATED CIRRHOSIS AND CRYPTOGENIC CIRRHOSIS**

In a study by Bugianesi, et al (23), 73% of 70 consecutive patients with cryptogenic cirrhosis were found to be obese, and 53% were diabetic. Indeed the above study showed histologic proof of NAFLD, or NASH, in about 65%–90% of patients with “cryptogenic” hepatitis. Thus NASH may be slowly progressive or may manifest as an acute exacerbation of previously unrecognized liver disease.

Al-Osaimi, et al (24) suggested that most, if not all, patients with cryptogenic cirrhosis were representative of a late stage of NASH.
OBESITY AND NAFLD/NASH

Ashraf, et al (25) analyzed liver biopsies of 40 asymptomatic obese patients with BMI 47 ± 9 and found that NASH and cirrhosis were present in 75% of patients without any clinical or biochemical evidence. Caldwell(26) reported on a small number of patients with a history of obesity who developed a subacute course of liver failure superimposed on undiagnosed NASH, 4–16 weeks from the onset of symptoms.

Ratziu, et al (27) also documented that obesity related cirrhosis can be progressive, resulting in liver failure and death. The authors showed that survival of patients with obesity-related cryptogenic cirrhosis was lower than age and sex matched patients with hepatitis C related cirrhosis. Hepatitis C related cirrhosis and hepatocellular carcinoma [HCC] was detected in a higher percentage of patients with obesity-related cirrhosis than in the matched hepatitis C cirrhosis controls.

Ohata, et al (28) documents that hepatic steatosis is an added risk factor for HCC in obese patients with chronic HCV infection. Thus patients with chronic HCV and hepatic steatosis should be monitored carefully for HCC.

CLINICAL ASSOCIATIONS

Patt, et al (29) reported that 243 of 1,178 executives undergoing routine assessments had elevated serum aminotransferases suggestive of NAFLD. And about half of patients with hyperlipidemia have been found to have NAFLD (30–32).

Liangounskul, et al (33) report that there is an association between hypothyroidism and NAFLD/NASH.

Some patients, particularly children may have acanthosis nigricans, which has also been associated with other insulin-resistant states. NAFLD is also associated with several disorders characterized by abnormal body fat distribution (lipodystrophies).

NAFLD is also associated with Inflammatory Bowel Disease [IBD]. Bargiggia, et al (34) reported liver steatosis in 39.5% of patients with Crohn’s Disease and 35.5% of patients with Ulcerative Colitis; a higher prevalence than among healthy controls.

A third of patients, mostly adults with NAFLD, are asymptomatic. More than half complain of fatigue and about a third complain of abdominal right upper quadrant [RUQ] discomfort. Less than half have hepatomegaly and only a small minority have any stigmata of liver disease, such as edema, jaundice, splenomegaly or ascites (35).

NASH is a significant cause of morbidity and mortality in patients with obesity-related type 2 diabetes (36). There is a strong association between hepatic steatosis and insulin resistance in humans (37) as well as experimental animals (38–41) in which evidence suggests that insulin resistance is the link among all the manifestations of the Metabolic Syndrome (38–41).

Insulin resistance is critically involved in the pathogenesis and progression from NAFLD to NASH. The model of genetically obese, ob/ob C57BL-6 mice was used in the Diehl study (42). This study provides a well-characterized model of hyperinsulinemia and insulin-resistance in which the animal’s hepatic steatosis mimics the evolution of fatty liver in obese human beings. These animals similarly experience hyperinsulinemia and increased insulin resistance. Insulin resistance is uniformly present in patients with NASH, including patients without diabetes. Day, et al describes “2 hits”[see below] in the pathogenesis of steatohepatitis (43). Argulo explored further details of NASH pathogenesis in his excellent review article in the NEJM, 2002;346:1221.

NASH AND THE METABOLIC SYNDROME

As noted, patients with NAFLD have a greater likelihood of developing NASH and hepatic fibrosis when insulin resistance and the Metabolic Syndrome are present.

Lopez-Canales, et al (44) believes that the Metabolic Syndrome [Syndrome X] should be considered when three or more of the following factors are present: a) central obesity with waist circumference >102 cm. in men; or 88 cm. in women; b) hypertriglyceridemia levels >150 mg/dL; c) HDL cholesterol under 40 mg/dL in men; and under 50 mg/dL in women; d) hypertension with BP >135/85 mm/Hg and; e) fasting glucose levels over 110 mg/dL. Many of these obese patients have hypertension and other abnormalities (45–49).

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Are there any clues in this panorama of hormonal events that will offer therapeutic option(s)? There are many more questions than answers. But much appears to be known mostly from animal studies. Human studies are not too far behind, mostly confirming (and sometimes conflicting). See Table 1 [compiled from references 50–71], and Table 2 [compiled from references 72–81, 83–96]. Both tables outlines available information in a condensed form.

**CLINICAL PRESENTATION**

While most patients with NAFLD are asymptomatic, a variety of nonspecific symptoms such as right upper...
Table 2 [compiled from references #72–81; 83–96]

<table>
<thead>
<tr>
<th>Evidence for Hormonal and Inflammatory Mediators in Insulin Resistance Leading to NAFLD/NASH</th>
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<tbody>
<tr>
<td>1. Liver Free Fatty Acids (FFA) levels can increase from excessive “importation” from adipose tissue [with rapid weight loss?], excessive carbohydrate and protein conversion to FFA causing triglyceride accumulation and steatosis [also with TPN?]; impaired beta-oxidation to ATP from Panthenic acid [Vitamin B5] deficiency, excessive alcohol intake, or coenzyme A deficiency [with use of valproic acid, aspirin]. Increased FFA is a risk factor for insulin resistance and type 2 diabetes and inhibits insulin-stimulated glucose uptake in patients with type 2 diabetes (72).</td>
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<td>2. Tumor necrosis factor-alpha (TNFα) reduces insulin sensitivity and has pro-inflammatory effects:</td>
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<td>A) A cytokine inhibits propagation of insulin receptor initiated signals in hepatocytes and promotes insulin resistance in ob/ob mice. Transgenic mice that are deficient in type-1 TNF receptors are completely protected from NASH (42).</td>
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<td>B) Increased release of TNFα from adipocytes impairs insulin action and increases insulin resistance which results in accumulation of hepatocytes fat and in turn leads to a vicious cycle of mitochondrial oxidation overload with further fat accumulation and increased impairment of mitochondrial electron flow, which with reactive oxygen species [ROS] causes expression of the Fas ligand which is associated with killing of hepatocytes (42,73–76). Furthermore studies show:</td>
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<tr>
<td>1) Administration of anti-TNFα antibody leads to marked improvement in glucose utilization in obese rats (73),</td>
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<td>2) Obese mice genetically lacking TNFα have more normal insulin sensitivity (74).</td>
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<td>3) Weight reduction in obese animals is associated with both improved insulin activity and decreased TNFα gene expression (75).</td>
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<td>4) TNFα plasma levels are positively correlated with insulin resistance (76).</td>
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<td>5) TNFα is a key factor in the inflammatory process that occurs in a variety of inflammatory disorders including NASH (42) and cirrhosis (78); is associated with increased mitochondrial oxidant production, and induces expression of uncoupling protein-2 (79).</td>
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<td>6) A fatty acid-binding protein in adipocytes, ap2, may provide the link by which FFA in obesity leads to increased expression of TNFα in obesity. Targeted mutations in the gene are associated with obesity, but not insulin resistance or increased TNFα expression (76).</td>
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<td>3. Uncoupling protein 2 (UCP2) is an inhibitor of insulin secretion. Its role is uncertain but may increase fatty hepatocyte injury in the presence of INF-alpha (80,81).</td>
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<td>4. Resistin is an adipocyte-secreted hormone that decreases insulin-mediated glucose uptake by adipocytes (83).</td>
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<td>5. Adiponectin another adipocyte-derived hormone has antilipogenic and anti-inflammatory effects. Reduced adiponectin levels are associated with more extensive necroinflammation. Deficiency of adiponectin, plays a role in the development of insulin resistance as evidenced by:</td>
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<tr>
<td>A) Low serum concentrations of adiponectin in humans are associated with an increased risk of type 2 diabetes (84).</td>
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<td>B) The degree of hypoadiponectinemia is more closely related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity and glucose intolerance (85).</td>
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<td>C) Administration of thiazolidinediones increase serum adiponectin concentrations without effecting body weight (86).</td>
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<td>D) In obese or lipotoxic mice, adiponectin administration decreases the degree of insulin resistance (87).</td>
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<td>E) In adiponectin-knockout mice, plasma and adipocyte concentrations of TNFα increase, which results in severe diet-induced insulin resistance (88).</td>
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<tr>
<td>F) Adiponectin increases insulin sensitivity perhaps by increasing tissue fat oxidation resulting in reduced circulating fatty acid levels and reduced intramyocellular or liver triglyceride content (89).</td>
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What is the evidence that adiponectin (or lack thereof) plays a role in pro-inflammatory mechanisms?

A) Human studies show reduced adiponectin link between adiposity, inflammation, and type 2 diabetes (90).
B) Decreases in plasma adiponectin are associated with low-grade chronic inflammation (91).
C) Low levels of adiponectin are associated with higher levels of two inflammatory mediators, hs-CRP and IL-6 (92).
D) Modulation by adiponectin of adipocyte function may be the mechanism by which thiazolidinediones (and not Metformin) influence insulin action (93).

6. Ghrelin is a hormone that is secreted primarily by the stomach and duodenum, and may increase food intake. Ghrelin is negatively correlated with leptin before gastric bypass surgery, but increases after diet-induced weight loss, suggesting a role in the compensatory (increasing) changes in appetite that make sustained diet-induced weight loss difficult (94). Ghrelin may play a role in determining the type of metabolic substrate [i.e. fat vs. carbohydrate] used for energy balance. (PNAS, 2004; 101:8227)

7. Acylation-stimulating protein (ASP) acts as a paracrine signal to increase the efficiency of triglyceride synthesis in adipocytes, which leads to increased postprandial lipid clearance. Genetic knockout of ASP leads to improved insulin sensitivity in mice and reduced body fat and obesity. Prior to human Roux-en-Y gastric bypass surgery ASP, insulin and leptin are elevated and adiponectin and ghrelin are decreased. After surgery, leptin and ASP decreases, adiponectin increases and insulin resistance improves—best predicted by an increase in adiponectin. These changes in ASP and adiponectin, in humans are predictive of decreased apolipoprotein B and improved insulin action, respectively (95,96).
quadrant or epigastric pain or discomfort, weakness, fatigue, and malaise may be present (97). Hepatomegaly is often the only suggestive physical finding (98). Levels of liver enzymes do not necessarily correlate with activity or severity of fat-induced liver disease (99). Significant NASH can be present in patients with normal liver enzymes and the only (if any) overt biochemical evidence of NAFLD can be minimal elevation of AST or ALT (100).

Clinicians should also be sure to at least think about other possible causes of NAFLD, such as rare disorders like Mauriac syndrome; metabolic and lipid disorders [e.g. abetalipoproteinemia, hypobetalipoproteinemia, Anderson’s Disease, Weber-Christian syndrome]; medication associated NAFLD [e.g. Amiodarone, Diltiazem, Tamoxifen, Steroids, and antiretroviral therapy] and occupational/environmental associations with NAFLD [e.g. toxic exposures to organic solvents and dimethylforamide]. NASH is also found with administration of TPN, rapid weight loss, acute starvation, excessive small bowel resection, gastroplasty, jejunal diverticulosis with bacterial overgrowth, plus jejunal and biliary-pancreatic diversion.

**ABNORMAL LIVER CHEMISTRIES**

Clark, et al (101) demonstrated that the prevalence of aminotransferase elevations in the USA is 7.9%. This is more common in Mexican-Americans (14.9%), and non-Hispanic Blacks (8.1%) compared to non-Hispanic Whites (7.1%).

The majority (69%) of aminotransferase elevations in the USA are unexplained, but are strongly associated with central adiposity and insulin resistance. Elevated AST or ALT levels are thought to be predictive of NAFLD if two basic criteria are met: 1) exclusion of alternative chronic liver disease with the most common being chronic hepatitis C and B, alcoholic liver disease, and hemochromatosis and the less common autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and 2) the presence of the Metabolic Syndrome.

However, it should be noted again that the entire histologic spectrum of NAFLD/NASH can be seen in individuals with normal and elevated ALT lab values. Thus a low or normal ALT does not guarantee freedom from underlying steatohepatitis with advanced fibrosis (102,105,106). The significance of iron accumulation is unknown but it has been sporadically reported in NASH. Most of these patients have elevated levels of ferritin and approximately 6% have an elevated transferrin saturation (103).

Reddy, et al (104) found that antinuclear antibody (ANA) titers are frequently detected in patients with NAFLD/NASH (37%). Earlier it was thought that ANA was not present in many patients. Thus it is important to rule out autoimmune hepatitis by liver biopsy where the clinical histories converge.

**AST:ALT RATIO**

The serum, AST:ALT ratio is usually <1 in fatty liver disease whereas the ratio in patients with alcoholic liver disease is usually >2 (107,105). Alkaline phosphatase is usually normal, but can be mildly raised especially if the patient has some fibrosis. Bilirubin is usually not abnormal except in late stages, as is albumin and the prothrombin time. Albumin, bilirubin and prothrombin time are usually normal in fatty liver disease in the absence of cirrhosis (107,108).

**DIAGNOSTIC EVALUATION**

The important questions in the standard of medical care for practicing physicians when evaluating patients

<table>
<thead>
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<th>Table 3 Causes of Chronically Elevated Aminotransferase Levels</th>
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<td><strong>Hepatic Causes</strong></td>
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<tr>
<td>- Alcohol abuse</td>
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<tr>
<td>- Medication</td>
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<tr>
<td>- Chronic hepatitis B and C</td>
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<tr>
<td>- Steatosis and nonalcoholic steatohepatitis</td>
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<tr>
<td>- Autoimmune hepatitis</td>
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<tr>
<td>- Hereditary Hemochromatosis</td>
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<tr>
<td>- Wilson’s disease (in patients &lt;40 years old)</td>
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<td>- Alpha1-antitrypsin deficiency</td>
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<tr>
<td><strong>Non-hepatic causes</strong></td>
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<td>- Celiac Sprue</td>
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<tr>
<td>- Inherited disorders of muscle metabolism</td>
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<tr>
<td>- Acquired muscle diseases</td>
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<tr>
<td>- Strenuous exercise</td>
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with chronically elevated liver chemistries (LFTs) are as follows:
1) In which patient is NAFLD and NASH suspect?
2) How is the diagnosis of NAFLD and NASH established?
3) When and how should one attempt to make a definitive diagnosis?
4) How and when does one treat the disease?
There is a wide spectrum of pathophysiologic causes that can result in chronically elevated aminotransferase levels. The more common non-NAFLD disorders are seen in Table 3. We prefer an initial stepwise diagnostic lab approach in patients with elevated AST, ALT levels seen in Table 4.
If these diagnostic tests are inconclusive one should consider the presence of fat-induced liver injury whose clinical findings are summarized in Table 4. Unfortunately, clinical symptoms as well as current laboratory and imaging technology usually cannot accurately differentiate between NASH and benign NAFLD.

### IMAGING STUDIES

Ultrasoundography has limited sensitivity and specificity for diagnosing NAFLD, but may detect the characteristic hypoechogenic areas. Unenhanced abdominal CT can reveal isolated areas of hypodensity or diffuse hypoechogenicity, often an “incidental finding” in a diagnostic study. Siegelman found that Magnetic Resonance Imaging (MRI), adds little to CT findings of diffuse steatosis (109).

Brandhagen, et al (110) compared the accuracy of ultrasound and CT scanning for the diagnosis of...
NAFLD. For ultrasound, the sensitivity was 50%, specificity 100%, and accuracy 85.7%; for CT scanning, the sensitivity was 17%, although specificity was 100%, and accuracy was calculated at 80.4%.

All imaging modalities, however, are limited by their inability to distinguish between non-progressive NAFLD, NASH and early fibrosis. The fact is that none of the above imaging techniques can give a definitive diagnosis of NASH. Indeed Saadeh, et al (111) in the largest and most in depth study of patients with pathologically proven NAFLD concluded from simultaneous radiological assessments taken shortly after biopsy with three different modalities that differences between NASH and non-progressive NAFLD were not apparent with any radiological modality.

Oh, et al (112) evaluated the role of serum markers of fibrosis in the non-invasive diagnosis of NASH vs. benign steatosis. Measurement of a marker designated as YKL40 showed a sensitivity and specificity (75% and 90%, respectively).

Sheth and Chopra (113) believe that a liver biopsy is indicated if any of the following clinical or laboratory features are present because of a higher likelihood of finding hepatic fibrosis. These include: 1) Peripheral stigmata of chronic liver disease, 2) Splenomegaly, 3) Cytopenia, 4) Abnormal iron studies, and/or 5) Diabetes in an individual over the age of 45.

However Vardar, et al (114) and Ong, et al (115) have concluded from their studies that there is no correlation of the above clinical or laboratory predictors of NASH or fibrosis.

Thus, until improvements can be made to current indirect marker techniques, there is no more accurate way to definitively establish a diagnosis of NASH than liver biopsy.

LIVER BIOPSY

Liver biopsy has become the most important diagnostic and prognostic modality and despite its own problems is the “gold standard.” Liver biopsy currently is the most sensitive and specific means for the accurate diagnosis of the NAFLD/NASH spectrum.

Clinically, the current standard of care is to perform liver biopsy for patients who have had undiagnosed consistently elevated LFTs for more than four to six months and/or have a working diagnosis or clinical factors favoring developing liver fibrosis.

The histologic presence of necrosis and fibrosis of NASH portends an adverse outcome of cirrhosis and death. Fibrosis on liver biopsy is a worrisome biopsy finding because it indicates increased risk of progression to cirrhosis. It is important to suspect NASH, and to obtain a definitive diagnosis in patients with persist-
tently elevated LFTs. Once the diagnosis of NASH is made, the standard of medical care calls for frequent monitoring in an effort to possibly prevent, or at least to detect earlier, NASH progressing to cirrhosis with its major complications.

Crespo, et al (116) analyzed 181 wedge liver biopsies at the time of bariatric surgery without knowledge of the patient’s clinical or biochemical data. The study authors found that no clinical nor biochemical abnormalities other than liver biopsy predicted progressive hepatic fibrosis in patients with NAFLD.

A study from researchers in Southwest England described a number of patients with NASH and follow-up liver biopsies (117). Interval histologic progression of NASH had occurred with development of cirrhosis and hepatocellular carcinoma in about two years. Harrison and colleagues (118) reported follow-up results of patients with liver biopsies diagnostic of NASH from 1985 and found that 30% of patients had interval increases in fibrosis on repeat biopsy.

Overall, the risks of liver biopsy are low (119). A retrospective study reviewed the mortality and morbidity of over 9,000 liver biopsies performed over a 20-year period and showed a 0.11% fatality rate and 0.24% risk of non-fatal hemorrhage (82). Studies have shown that image guided liver biopsies are associated with even more marked reduction in bleeding and hypotension episodes, compared to percutaneous liver biopsy (120).

Although percutaneous liver biopsy is sometimes a painful procedure it has been shown that mild anxiolytic treatment plus local anesthetic infiltration seems to produce sufficient analgesia (121). Smith, et al (122) demonstrated the use of an automated core biopsy needle via the transjugular approach in those patients with contraindications to percutaneous hepatic biopsy (coagulopathy and/or ascites). This study yielded 98% of adequate tissue specimens and showed a complication rate of 2.4% with one death in 371 patients who underwent 409 procedures.

Fibrosis may not be as irreversible as once was thought (123). Perhaps early and effective diagnosis and treatment of NASH will decrease the progression of fibrosis as documented by Poynard, et al (124) in therapeutic trials of patients with hepatitis C-induced liver fibrosis. Early definitive recognition of NASH and fibrosis by biopsy has the theoretical advantage of providing the impetus for both the patient and the physician for more intensive medical monitoring and aggressive treatment aimed to improve histology and prevent progressive liver disease. This will hopefully decrease the number of patients who develop decompensated cirrhosis and have to be considered for liver transplantation.

An important incentive for early diagnosis and aggressive treatment of NASH has been documented by Bugianesi, et al (125). Features suggestive of NASH were more frequently observed in hepatocellular carcinoma (HCC) arising in patients with cryptogenic cirrhosis than in age- and sex-matched HCC patients of well-defined viral or alcoholic etiology. According to these authors, HCC may represent a late complication of NASH-related cirrhosis. We have no evidenced based data, however, to prove that any treatment will prevent cancer nor even that NAFLD can be prevented from progressing to NASH and cirrhosis.

References

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