

brate, despite its lipid-lowering effects, was not beneficial. The potential efficacy of UDCA in patients with NAFL is currently being investigated in a randomized, controlled clinical trial.

## SUMMARY

NAFL is a common liver disease characterized by asymptomatic and mild elevation of aminotransferases in the absence of excessive alcohol use or other liver diseases. NAFL encompasses a spectrum of clinico-pathologic entities with the common feature of fatty accumulation and histologic appearance similar to that of alcohol-induced liver disease. This spectrum ranges from simple steatosis to steatohepatitis and steatonecrosis.

The subtypes of NAFL showing hepatocyte ballooning and necrosis, with or without Mallory hyaline and fibrosis, carry a risk for cirrhosis. Conversely, steatosis alone does not seem to be progressive and most likely has a benign course. Since clinical data alone cannot predict the course of NAFL, histological features found on the liver biopsies may be important for staging and prognosis, especially in young people and those with diabetes mellitus.

Although no definitive therapy for NAFL exists, UDCA, antioxidants (vitamin E), weight reduction, and treatment of hyperinsulinemia are currently being investigated.

As the prevalence of obesity in the western world increases, NAFL has the potential to become one of the most common types of liver disease. The goal of NAFL research must be to clarify the pathogenesis of the aggressive form of NAFL and to design therapeutic interventions that can change the course of the potentially aggressive forms of this disease.

## Publications and Presentations

### Publications

- S Saadeh, G Cammell, K Easley, **Z Younossi**, W Carey. Role of Liver Biopsy In Chronic Hepatitis C. *Hepatology* 2000, 33(1):196-200
- **Z Younossi**. Viral Hepatitis Guide to Practicing Physicians. *Cleve Clin J Med* 2000, 67, Supple 1:SI6-45
- Duchini A, **Z Younossi**, A Saven, G Bordin, H Knowles, P Pockros. An open-label pilot trial of Cladribine (2-CdA) in patients with primary sclerosing cholangitis. *Clin J of Gastro* 2000, 31(4):292-296.
- **Z Younossi**, M Kiwi, N Boparai, G Guyatt. An in Depth Assessment of Quality of Life in Chronic Cholestatic Liver Disorders. *Am J of Gastro*, Vol 95 (No. 2):497-502, 2000.
- **Z Younossi**, N Boparai, M McCormick, G Guyatt. Assessment of Utilities and Health-Related Quality of Life in Chronic Liver Diseases. *Am J of Gastro*, Vol 95 (No. 2): 2001
- **Z Younossi**, M McCormick, N Boparai, L Farquhar, J M Henderson, G Guyatt. The Impact of Liver Transplantation on Health-Related Quality of Life. *Liver Transplantation* 2000; 6:779-783.

### Presentations

- American College of Gastroenterology Post-Graduate Course, 65th Annual Meeting, New York, NY
  - Update on Non-Alcoholic Steatohepatitis at the ACG postgraduate course
  - Symposium on Non-Alcoholic Steatohepatitis during the 65th ACG annual meeting
- Presentations at the 51st annual meeting of American Association for the Study of Liver Diseases, Dallas, TX
  - Two early breakfast session on Non-alcoholic Steatohepatitis (co-moderator)
  - Meet-the-professor meeting on Hepatitis C and health-related quality of life
- Poster Presentations at the 51st annual meeting of American Association for the Study of Liver Diseases, Dallas, TX
  - Hepatocellular Carcinoma, Hepatitis C and Ethnicity
  - Combination of Interferon (2b, Ribavirin and Amantadine for Hepatitis C Treatment Failures
  - A Disease-Specific, Health-Related Quality of Life Instrument for Chronic Hepatitis: CLDQ-HCV

## OPEN PROTOCOLS

The following protocols are open for patient enrollment at the Center for Liver Diseases:

- Pegylated Interferon alfa 2b and Ribavirin for chronic hepatitis C, previous treatment failures.
- Triple regimen of Pegylated Interferon alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C; treatment failures or naïve.
- Adefovir dipivoxil for the treatment of hepatitis B; untreated or with YMDD variant.
- Pegylated Interferon alfa 2a (PEGASYS) alone or in combination with Ribavirin for chronic hepatitis C; treatment failure or naïve.
- Immunomatrix Evaluation of a rapid one step immunoassay for HCV.

For patient screening or additional information, please call Peggy Kraft at **703-204-6491** or the Center for Liver Diseases, **703-698-3182**.

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## Dr. Sharieff Joins Inova Transplant Center

Khavir Sharieff, DO, has joined the Inova Transplant Center at Inova Fairfax Hospital as a transplant surgeon. He received a bachelor's degree from George Washington University and attended medical school at Des Moines University, Iowa. He received a Doctor of Osteopathy degree in 1993 and completed a general surgery residency at Wyckoff Heights Medical Center in Brooklyn, NY.

Dr. Sharieff then served a multi-organ transplant fellowship at Albert Einstein Medical Center, Philadelphia, where he trained in the areas of hepatobiliary surgery, liver, kidney and pancreas transplantation.

Dr. Sharieff's interests are liver regeneration and allograft tolerance post transplantation. He is also interested in studying the impact and long-term outcome of marginal donor organs and allo-immune responses.

In his free time, Dr. Sharieff enjoys hiking, mountain biking, swimming and tennis. He also enjoys reading early Urdu writing and literature.

"My long term goal is to be an excellent multi-organ transplant surgeon dedicated to transplant patient care and research," he said.

Inova Health System is a not-for-profit health care system in Northern Virginia that consists of hospitals and other health services including home care, nursing homes, mental health services, physician practices, wellness classes, and freestanding emergency and urgent care centers. Governed by a voluntary board of community members, Inova's mission is to provide quality care and to improve the health of the diverse communities we serve.

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# Liver Update

*A publication of the Center for Liver Diseases and the Inova Transplant Center*

## An Update on Non-Alcoholic Steatohepatitis

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Non-alcoholic steatohepatitis (NASH) is a relatively common liver disease in which people who drink little or no alcohol have histologic liver abnormalities similar to those found in alcoholic hepatitis. NASH is now known to be just one of a spectrum of non-alcoholic fatty liver diseases (NAFL), which includes steatosis alone, steatosis with non-specific inflammation, steatonecrosis and steatohepatitis.

All of these non-alcoholic fatty liver diseases are characterized by elevation of aminotransferases in the absence of excessive alcohol use or other liver diseases. NAFL is more common in the obese and in type II diabetics, but has recently been shown to include disease occurring in non-diabetics and lean individuals. Additionally, different types of NAFL have been linked with other conditions such as jejunioileal bypass, intestinal resection, limb lipodystrophy, abetalipoproteinemia, and Weber-Christian disease, and with drugs such as amiodarone, perhexiline maleate, glucocorticoids, synthetic estrogens and tamoxifen. In this article, I will discuss the clinical importance of NAFL, prognosis, risk factors, diagnosis and treatment.

### THE CLINICAL IMPACT OF NAFL

The impact of NAFL relates to its prevalence and its potential for progression to cirrhosis. The prevalence of NAFL in general population has yet to be defined. In autopsy series of airplane crash and motor vehicle accident victims, the prevalence of fatty liver was estimated at three percent. In these series, simple steatosis was not clearly distinguished from NASH.

In another autopsy series of more than 250 patients, the prevalence of steatonecrosis in lean individuals was approximately three percent, while in the obese, the rate was approximately 19 percent. Prevalence may be as high as 20 to 50 percent in certain high-risk populations such as those with type II diabetes mellitus and obesity. These reasons may contribute to the fact that NAFL appears to be more common in western countries. In the clinical setting, NAFL is one the most common reasons for chronically elevated aminotransferases in an asymptomatic individual. It is important to remember that as obesity has become more prevalent, the prevalence of NAFL will certainly increase, making it potentially one of the most common forms of liver disease in the United States.

The potential of NAFL to progress to advanced liver disease and cirrhosis is also a matter of debate. There are significant discrepancies in the literature that can be attributed in part to the variability in the pathologic definition of NASH, the

*see NASH, page 2*

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amount of alcohol consumption required to exclude alcohol-related fatty liver disease, the exclusion of other confounders (such as hepatitis C virus [HCV] and iron overload) and the lack of sequential biopsies or long-term follow-up.

The potential course of NAFL also remains poorly defined. Although earlier reports suggested a benign and non-progressive course, a recent aggregation of data from the literature showed that approximately 8 to 17 percent of patients with NASH progress to cirrhosis over one to seven years.

In summary, NAFL may be one of the most common forms of liver disease in the U.S. Although steatosis alone seems to be benign, patients whose hepatic steatosis is accompanied by ballooning degeneration, hepatocyte necrosis and fibrosis may progress to cirrhosis and end-stage liver disease.

### THE PATHOGENESIS OF NAFL

The pathogenesis of NAFL is not entirely clear, but several theories have been proposed. These include abnormalities in hepatic lipid peroxidation, Kupffer cell dysfunction and more recently, abnormalities of mitochondrial uncoupling proteins. Regardless of the exact mechanism, it is postulated that oxidative stress plays a central role in the pathogenesis of aggressive NAFL.

### EVALUATING PATIENTS WITH SUSPECTED NAFL

Typically, patients with NAFL present with asymptomatic and incidental elevation of aminotransferases or hepatomegaly. They may also experience fatigue, malaise, vague right upper quadrant abdominal pain and other non-specific symptoms. Although NAFL typically presents in the fourth decade of life, some

patients present as early as the first and second decades.

In evaluating an individual for NAFL, a strict history of alcohol use should be obtained. When evaluating patients, it is also important to remember that NAFL is a diagnosis of exclusion. Other forms of liver disease (chronic viral hepatitis, Wilson's disease, autoimmune hepatitis, etc.) must be considered and excluded with appropriate laboratory tests. In a young patient, Wilson's disease can masquerade as fatty liver.

As type II diabetes and hyperlipidemia are associated with NAFL, the patient should also be assessed for these conditions during the initial evaluation.

### LIVER BIOPSY AND HISTOLOGY FOR DIAGNOSIS

Liver biopsy remains the gold standard for the diagnosis of NAFL because it can be used to distinguish the various histologic subtypes (steatosis alone, steatohepatitis, steatonecrosis, etc.). This information may be especially important for staging the liver disease and may provide prognostic information about the potential course of the liver disease.

Although pathology is generally recognized as important, there has been a lack of agreement on the exact pathologic features required to establish the diagnosis of NASH and the other subtypes of NAFL. Although the term NASH has received the widest acceptance, it is important to remember that steatohepatitis literally means fat accumulation plus inflammation. This pathologic description is quite different from the pathologic entity NASH, which is defined as increased fatty accumulation with hepatocyte ballooning, necrosis, and/or fibrosis.

It is also important to remember that other pathologic subtypes of NAFL

(steatosis alone, steatonecrosis and histologic alcoholic-like hepatitis) are also included in this pathologic spectrum. The exact features required for the pathologic diagnosis of each type of NAFL are not totally clear. In one study, steatosis alone was defined as fat accumulation alone, whereas steatonecrosis required fat accumulation, hepatocyte necrosis and ballooning degeneration.

In summary, although liver biopsy provides important prognostic information, its role in management and diagnoses of NAFL remain unsettled. It is clear that liver biopsy is essential in clinical research of NAFL and that it plays a central role in defining progression over time. In clinical practice, the widespread use of liver biopsy is controversial but should be considered in young patients (especially those with type II diabetes) and those patients who show no change after reversal of their associated risk and conditions.

### MANAGING NAFL

The main goal of therapy for NAFL should be to prevent progression to cirrhosis. Unfortunately, although a variety of treatment modalities have been proposed, none has proven efficacy in changing this endpoint. Treatment modalities such as weight reduction program for obese patients may be beneficial. Treating hyperlipidemia and diabetes are probably also important, but the value of these therapies remains to be established.

Ursodeoxycholic acid (UDCA) and antioxidants (vitamin E) have recently been proposed as medical therapies for NAFL. In one study, patients with NASH treated with a 12-month course of UDCA showed a significant improvement of liver enzymes and a reduction in hepatic steatosis. In contrast, clofi-

*see NASH, page 5*

# An Update on Genetic Hemochromatosis

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Genetic hemochromatosis is a common inherited disorder present in three to five persons per 1,000 population of North European ancestry. The disease results from abnormal/excessive absorption of iron and accumulation in a variety of organs, including the liver, causing chronic liver disease and cirrhosis. The accumulation of body iron stores is correlated with age in genetic hemochromatosis and there is a threshold of hepatic iron concentration for the development of fibrosis and cirrhosis that may vary amongst patients.

Early detection and treatment of the genetic homozygote will prevent the development of tissue damage and will maintain normal longevity.

Confirmation of iron overload in the presymptomatic, precirrhotic stage of the disease is the indication for early removal of excess iron stores by phlebotomy. Phenotypic detection of the

**Table 1. Diagnosis of Iron Overload**

DIAGNOSTIC TEST	CATEGORY OF PATIENT	
	SYMPTOMATIC	ASYMPTOMATIC
<b>Indirect</b>		
Transferrin iron saturation	↑	nl or ↑
Serum ferritin	↑	nl or ↑
<b>Direct</b>		
Quantitative liver iron*	↑	↑
Phlebotomy assay*	↑	↑
HFE genotypes**	3	3

\* performed when indirect tests are positive

\*\* provides means for comparing proband with first degree relatives: confirms homozygosity

genetic homozygous state is best accomplished by screening for the serum transferrin iron saturation and should be confirmed by quantitative hepatic iron determination in certain circumstances (see algorithm). (Table 1,2)

Liver biopsy is valuable both for quantitative iron determination and for documentation of end-organ damage, and also to distinguish alcoholic liver disease with mild iron overload from

hemochromatosis in an individual who coincidentally abused alcohol.

The gene has been localized to chromosome 6 in proximity to the HLA A3 histocompatibility locus. In 1996, the mutated hereditary hemochromatosis gene was identified (termed HFE gene), and the causative mutation (Cys 282 Tyr) determined.

see Hemochromatosis, page 4

**Table 2. Diagnosis of Iron Overload\*\*\***

TEST	HOMOZYGOUS		HETEROZYGOUS HHC+	ALD	NORMAL
	FIBROSIS OR CIRRHOSIS	PRE- CIRRHOSIS			
Transferrin-iron saturation (%)	45-100%	33-100%	Up to 95%	Up to 60%+	20-45%
Serum ferritin (ng/ml)	1000-5000	40-4200	Up to 800	Up to 1000	15-250
Hepatic iron concentration g/g dry wet mol/g dry wet	14,000-37,500 250-670	1500-28,000 27-500	Up to 3500 Up to 63	Up to 6500 Up to 116	280-1500 5-27
Hepatic iron index (mol/g dry weight divided by age [y])	> 2	> 1.9	< 1.8	< 1.65	< 1

HHC, hereditary hemochromatosis; ALD alcoholic liver disease

\* Composite figures from Powell et al, 1990; Summers et al, 1990; Sallie et al, 1991 & Bassett et al, 1986

\* Twenty-five percent of heterozygotes have tests between the upper limit of normal and these maximum observed measurements

\*\* May be higher in the presence of active hepatic necrosis

The pathophysiologic effect of homozygosity for the hemochromatosis allele is the continued, excessive intestinal absorption of dietary iron. Sustained high transferrin iron saturation is the mediator of parenchymal iron deposition in genetic and secondary hemochromatosis.

Genotyping of first degree relatives of patients with hemochromatosis helps to determine the extent of their risk for the development of symptomatic disease. Only genetic homozygotes progress from positive indirect markers to significant tissue iron overload.

Establishing timely diagnosis of hemochromatosis results in administer-

ing an effective and safe therapy. Treatment includes therapeutic phlebotomy. This should start as initial de-ironing phase with 450cc phlebotomy weekly or biweekly to bring down the ferritin to around 25-50 ng/ml. This should be followed by a maintenance phase that could vary, but generally requires 450cc phlebotomy every three to four months.

### Proposed Algorithm for Management of HH

