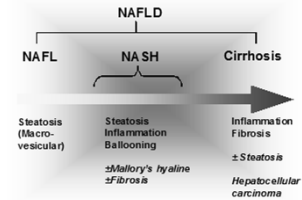


Definition of NASH

Nonalcoholic steatohepatitis (NASH) is the term used to describe the distinct clinical entity in which patients lack a history of significant alcohol consumption but have liver biopsy findings indistinguishable from alcoholic hepatitis.



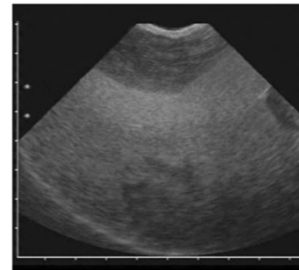
Criteria for Dx of NASH

- Liver bx shows macrovesicular fatty change with inflammation and with or without Mallory bodies, fibrosis or cirrhosis.
- Convincing evidence of negligible alcohol consumption (less than 10 g/day of alcohol for women and less than 20 g/day for men).



Ultrasound showing

Bright echogenic liver

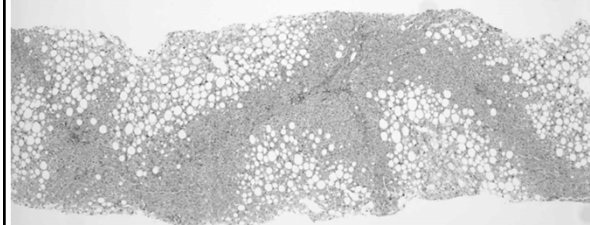


Liver Ultrasound Report

The liver is enlarged. It is diffusely echogenic consistent with fat infiltration of the liver. Other forms of liver disease and more advanced liver disease including early cirrhosis cannot be excluded by this study.

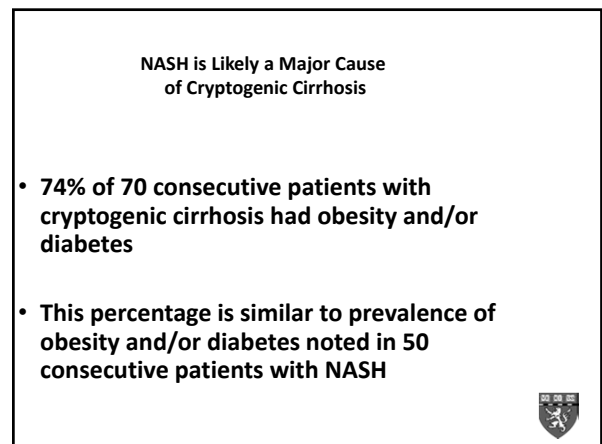
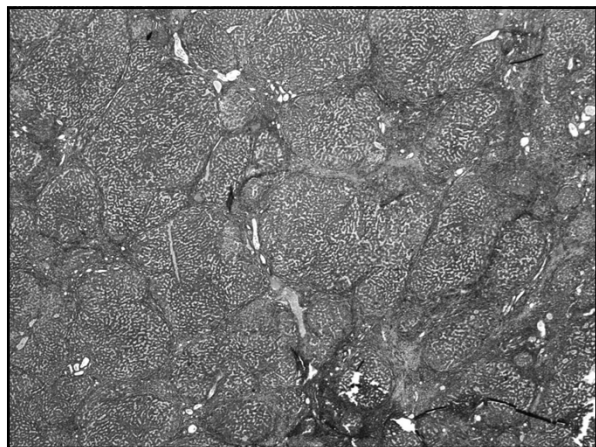
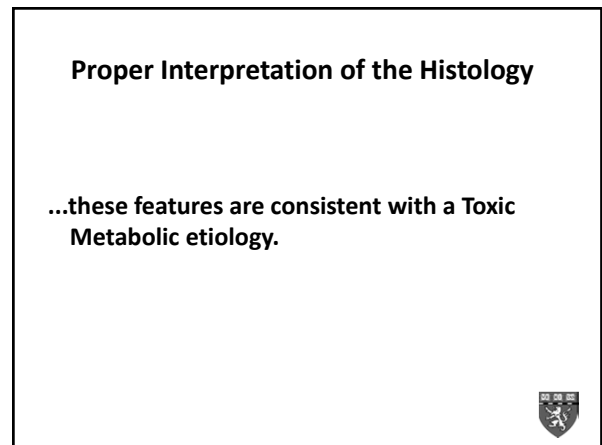
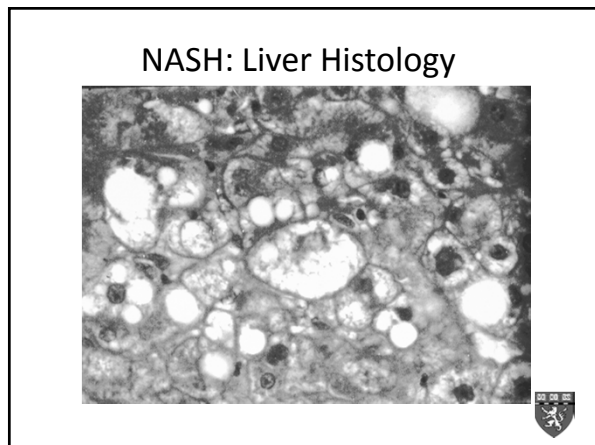
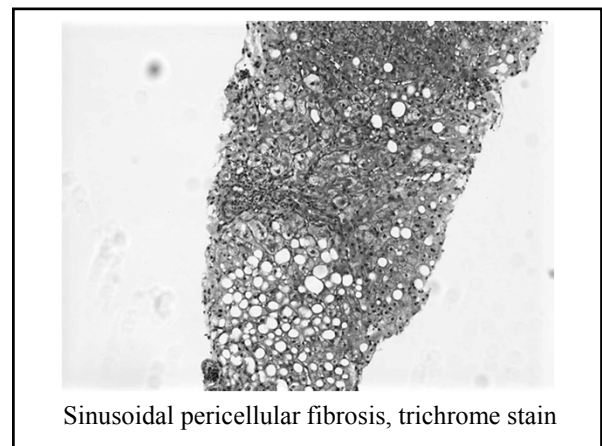
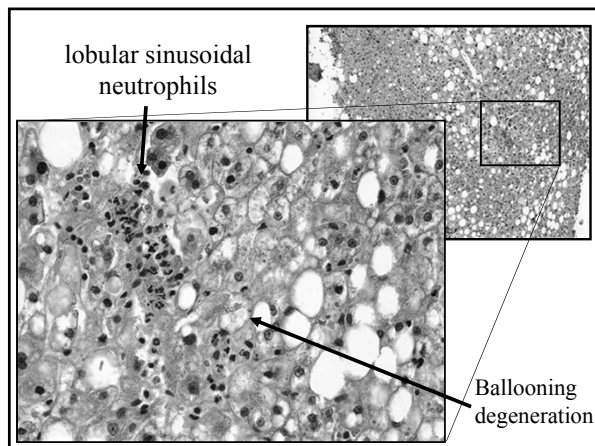


Biopsies



macrovesicular steatosis (zone III)





Epidemiology of NAFLD

- Estimate: **40 million** Americans have **NAFLD**
5 million are **cirrhotic**
- Majority of Pts with NASH have metabolic syndrome
- Over age 60 years, 40% have metabolic syndrome



NAFLD is Part of the Metabolic Syndrome Called Syndrome X

Obesity	Hypertriglyceridemia
Hyperinsulinemia	Hypertension
Insulin Resistance	Diabetes



Regular sugar-sweetened beverage consumption is associated with a greater risk of fatty liver disease

- Examination of cross-sectional association between intake of sugar-sweetened beverages and fatty liver disease in Framingham Heart Study cohorts

J Ma *et al.*, *Journal of Hepatology* 2015 May 29



Patients with NASH

	Normal ALT	Increased ALT	p.value
Fibrosis Stage 2 or greater	22%	34%	NS

Fracanzani AL, et al.
Hepatology 2008;48;792



Other Conditions Associated with NASH

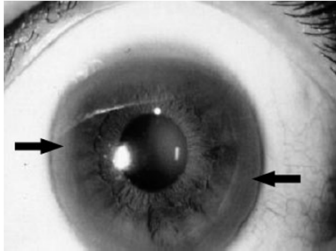
- Drugs or Toxins • Abdominal Surgery
- Metabolic Disorders • Miscellaneous



One disorder that is **critical** to exclude in young individuals is **Wilson's disease**



K-F Ring



Drugs Associated with NASH

- Glucocorticoids
- Tamoxifen
- Synthetic estrogens
- Perhexilene maleate
- Amiodarone
- Isoniazid



	Progression to Cirrhosis	10 Yr Survival
Alcoholic Hepatitis	38 – 50%	20%
NASH	8 – 26%	60%



NAFLD likely increases risk for cardiovascular mortality

- Pro-inflammatory, procoagulant factors and genes involved in accelerated atherogenesis are expressed in patients with NASH
- Longitudinal study of 1,872 patients
 - 12% developed steatosis
 - 23% developed carotid plaques
- Patients at cardiovascular risk presenting with one or more metabolic syndrome characteristics are at even greater risk if they have steatosis
- Cardiovascular disease is the leading cause of death in NAFLD patients

Adams LA and Anstee QM. *J Hepatol*. 2016.
Pais R, et al. *J Hepatol*. 2016



Clinical Features of NASH

Symptoms

- Asymptomatic
- Fatigue
- RUQ Discomfort or Pain



Laboratory Features of NASH

- ALT and AST 2 to 4 fold elevated in most patients
- Alk phos mildly elevated in a third of patients
- Albumin, PT, bilirubin most often normal
- Serum ferritin elevated in half the patients



Patients with Suspected NASH should Undergo Liver Biopsy

Pros

- NASH is a histologic dx
- Poor correlation between lab findings and histologic severity
- Biopsy results may change management

Cons

- Small but finite risk of complications
- Biopsy results may not change management
- Limited manpower



Suspected NASH: Reasonable to perform liver biopsy

If any of following present

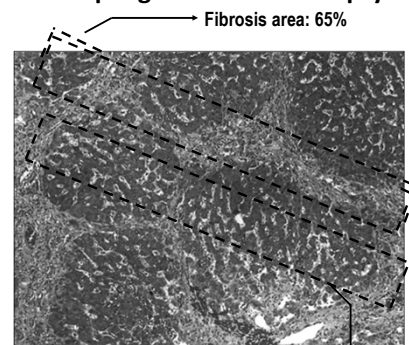
- Peripheral stigmata of chronic liver disease
- Splenomegaly
- Cytopenia
- Abnormal iron studies
- Diabetes and/or significant obesity in a patient over 45 years of age with elevated ALT



Are there alternatives to liver biopsy?



Sampling error of liver biopsy



Fibrosis area: 15%

Fibrosis area: 65%

Courtesy of M. Pinzani, Florence



Fibrotest (fibrosure)

Alpha 2 macroglobulin, haptoglobin, gammaglobulin, GGT, total bilirubin, apolipoprotein A1

The severity of disease was correctly identified in 46% of patients.

Am J Gastroenterol 2006

Fibrosure. I am not so sure!



Fibroscan

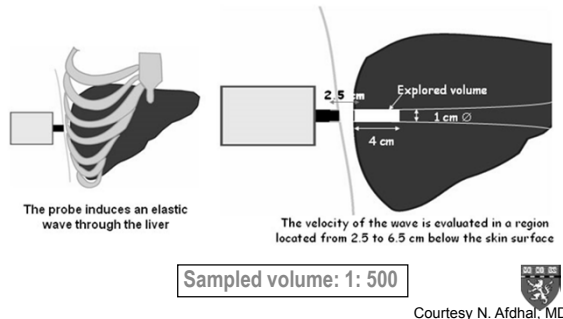
- Non-fasting
- Examination time < 5 minutes
- Median value of 10 successful acquisitions
- Sampling error
 - Biopsy – 1/50,000
 - Fibroscan – 1/500

Courtesy of N. Afdhal, MD



Hepatic Elastography

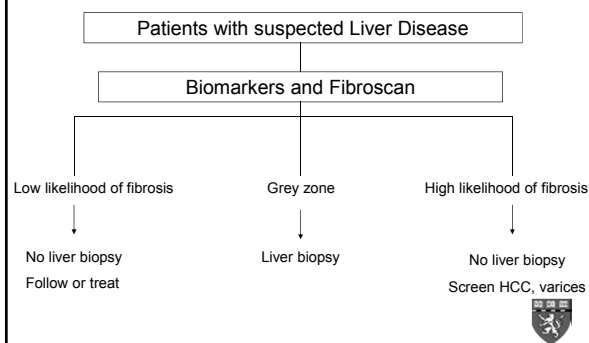
- Fibroscan is a rapid and non-invasive measure of hepatic stiffness
- Hepatic stiffness correlates with fibrosis



Sampling

- Liver biopsy samples only 1/50,000th of whole liver.
- Fibroscan samples 1/500th of whole liver.

Likely Future Scenario



Transient elastography (Fibroscan) is accurate in most patients with NAFLD. With high negative predictive value and modest positive predictive value, Fibroscan is useful as a screening test to exclude advanced fibrosis.

Wong V W-S, et al.
Hepatology 2010; 51:454-462

Progression of NAFLD

Initial Biopsy Results May Be Useful

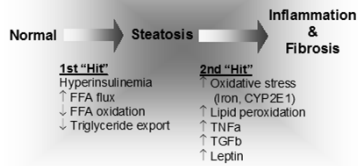
- Fat Alone Progression to Cirrhosis 5%
- Ballooning Degeneration and Mallory Hyaline or Fibrosis Progression to Cirrhosis 25%

Gastroenterology: 1999;116:1413

Pathogenesis of NASH

- Perturbation of fatty acid processing.
 - Insulin resistance
 - Lipid peroxidation and oxidative stress*
- * Potential oxidative stressors include: hepatic iron, intestinal bacteria, leptin and states characterized by anti-oxidant deficiencies

Pathogenesis of NAFLD/NASH The "Two Hit" Hypothesis



Definition

The concept of the human microbiome was first suggested by Joshua Lederberg, who coined the term "microbiome, to signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space".

Welcome to Boston
Population: 650,000

Welcome to Gut
Population: 100 trillion

The Gut Microbiota and NAFLD

- Microbiota in addition to regulating body fat gain and insulin resistance:
 - Change gene expression
 - Increase energy harvest from diet
 - Produce ethanol
 - Affect inflammation and immunity

E Lau *et al.* Gut Microbiota: Association with NAFLD and Metabolic Disturbances. Biomedical Research International. 2015.

Prevention and Treatment of NASH

- Prevention of obesity and metabolic syndrome
- Treatment of metabolic syndrome
- Coffee ?
- Bariatric Surgery if appropriate

Pioglitazone therapy over a 12 month period in nondiabetic NASH patients resulted in improvement in biochemical, metabolic and histological parameters (including fibrosis).

Aithal GP, et al.
Gastroenterology 2008: 135;1176

NASH: Weight Loss is Beneficial !

1. 9% or greater weight loss resulted in:
 - Biochemical improvement
 - Histologic improvement (steatosis, ballooning, inflammⁿ)
 - Improvement in Insulin resistance
 - Higher Adiponectin levels
2. Following bariatric surgery, Hepatic Fibrosis improved or was reversed in 66%.

Harrison SA, et al.
Hepatology 2009;49:80

Furuya CK Jr., et al.
J Gastro Hepatol 2007;22:510



Vitamin E May Have Benefit but Caution...

- 247 Adults with NASH (without diabetes) randomly assigned to pioglitazone (30 mg. daily) Vitamin E (800 IU daily) or placebo for 96 weeks*.
- Vitamin E group had significant improvement in global histology scores compared with placebo (43% vs 19%).
- Concerns regarding Vitamin E and increased mortality have led many Hepatologists to not recommend Vitamin E or to use 400 IU daily.

* Sanyal, A, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010



Other Pharmacological Treatment Modalities

- | | |
|----------------|-------------------------------|
| • Pioglitazone | • Ursodeoxycholic acid (UDCA) |
| • Metformin | • Omega-3 Fatty Acids |
| • Liraglutide | • Losartan |
| • Orlistat | • Atorvastatin |
| • Probuco | • Pentoxifylline |
| • Betaine | |

Of limited or no proven efficacy



Mechanism of Protective Effect of Coffee Unknown

- Caffeine, cafestol and kahweol protective in experimental studies
- Antioxidant effect
- Insulin sensitizing effect
- Coffee drinkers have higher levels of plasma adiponectin



More than 1 Billion People in the World Have Chronic Liver Disease

Consuming two cups of coffee per day reduces hospitalization rate and mortality from chronic liver disease by more than 50%

Ruhl CE, et al. Gastroenterology 2005;129:1928



References: Coffee and Liver Disease, 2012 Sanjiv Chopra, MD, MACP

1. Klatsky A, Armstrong M. Alcohol, smoking, coffee and cirrhosis. Am J Epidemiol. 1992;136:1248.
2. Casiglia E, et al. Unexpected effects of coffee consumption on liver enzymes. Eur J Epidemiol. 1993;9:293.
3. Tverdal A, Skurveit S. Coffee intake and mortality from liver cirrhosis. Ann Epidemiol. 2003;13:419.
4. Shimazu T, et al. Coffee consumption and the risk of primary liver cancer; pooled analysis of two prospective studies in Japan. Int J Cancer. 2005;10:150.



5. Ruhl CE, Everhart J. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. *Gastroenterology*. 2005;129:1928.

6. Klatsky AL, Morton C, Udaltsova N, Friedman G. Coffee, cirrhosis, and transaminase enzymes. *Arch Intern Med*. 2006;166:1190.

7. Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, Jousilahti P. Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer. *Hepatology*. 2008;48(1):129-36.

8. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology*. 2007;132(5):1740-5.



9. Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A; Collaborative SIDECIR Group. Coffee, caffeine, and the risk of liver cirrhosis. *Ann Epidemiol*. 2001;11(7):458-65.

10. Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? *Ann Epidemiol*. 2002;12(3):202-5.

11. Schilter B, Perrin I, Cavin C, Huggett AC. Placental glutathione S-transferase (GST-P) induction as a potential mechanism for the anti-carcinogenic effect of the coffee-specific components cafestol and kahweol. *Carcinogenesis*. 1996;17(11):2377-84.

12. Gelatti U, Covolo L, Franceschini M, Pirali F, Tagger A, Ribero ML, Trevisi P, Martelli C, Nardi G, Donato F; Brescia HCC Study Group. Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study. *J Hepatol*. 2005;42(4):528-34.



13. Modi AA, Feld JJ, Park Y, Kleiner DE, Everhart JE, Liang TJ, Hoofnagle JH. Increased caffeine consumption is associated with reduced hepatic fibrosis. *Hepatology*. 2010;51(1):201-9.

14. Kalthoff S, Ehmer U, Freiberg N, Manns MP, Strassburg CP. Coffee induces expression of glucuronosyltransferases by the aryl hydrocarbon receptor and Nrf2 in liver and stomach. *Gastroenterology*. 2010;139(5):1699-710.

15. Freedman ND et al. Coffee consumption is associated with response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. *Gastroenterology* 2011; 140: 161-69.

16. Molloy JW, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology*. 2012;55(2):429-36.



Large prospective study; Coffee consumption inversely associated with total and cause-specific mortality.

- Freedman, ND Ph.D., Park, Y Sc.D., Abnet, CC Ph.D., et al. **Association of Coffee Drinking with Total and Cause-Specific Mortality** *N Engl J Med* 2012; 366:1891-1904



“Coffee is so good, the infidels should not have exclusive use of it.”

Pope Vincent III



Potential Approaches to Treatment in the Future

- Will likely include combination therapy and life-style changes.
- Experimental study in a rat model of NASH combining angiotensin II receptor blocker with an oral iron chelator attenuated progression.
- Moderate exercise and coffee consumption likely of benefit.



NAFLD Treatment Future Horizons

Caspase Inhibitors

Modulation of Enzymes that play a role in inflammation

Safer and more effective Farnesoid x- receptor agonists

Novel targeting strategies based on understanding of various polymorphic genes



Patients with Elevated Transaminases are not at Higher Risk for Statin Hepatotoxicity

	Mild-Moderate Elevations	Severe Elevations
• 1439 with normal transaminases prescribed a statin	1.9%	0.2%
• 342 with elevated transaminases prescribed a statin	4.7%	0.6 %
• 2245 with elevated transaminases <u>not</u> prescribed a statin	6.4%	0.4%

Chalasani et al: Gastroenterology 2004;126



Obeticholic Acid (OCA) Treatment

- OCA is a semisynthetic bile acid analogue and a Farnesoid X Receptor (FXR*) ligand
- 283 patients with NASH enrolled in a OCA 25 mg p.o. vs. Placebo trial for 72 weeks
- In January 2014, trial stopped on basis of interim efficacy analysis

*FXR is a key player in control of multiple metabolic pathways – bile acids, glucose, lipids



Quiz Answer True or False

1. NAFLD is the most common hepatic disorder in the U.S.
2. Serum ferritin is elevated in 50% of pts with NASH.
3. NASH has been reported in children.
4. Progression to cirrhosis occurs in 15-20% of pts.
5. NASH is likely the leading cause of cryptogenic cirrhosis.



Quiz (Continued) Answer True or False

6. The histologic features of NASH maybe seen in Wilson's disease.
7. Both Amiodarone and Tamoxifen can cause NASH.
8. Primary hepatocellular carcinoma has been reported in patients with NASH and cirrhosis.

