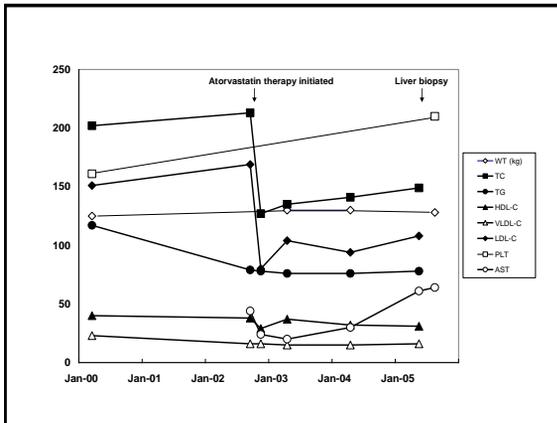


NAFLD and NASH: Metabolic Syndrome of the Liver

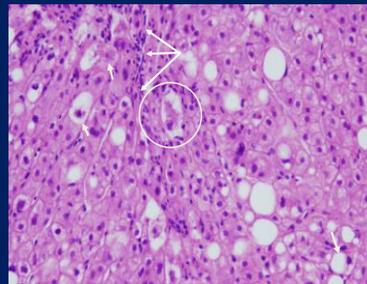
Curtis K. Argo, MD, MS
Assistant Professor
Gastroenterology and Hepatology

Statins and NASH: Case

- 58 year-old man with metabolic syndrome (obesity, HTN and hyperlipidemia)
- 3-year history of atorvastatin therapy



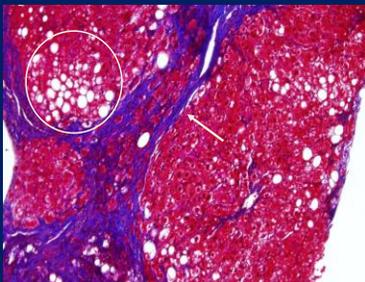
Statins and NASH: Case



Biopsy #1:

- Ballooned cells
- Lobular inflammation
- Mallory-Denk body

Statins and NASH: Case



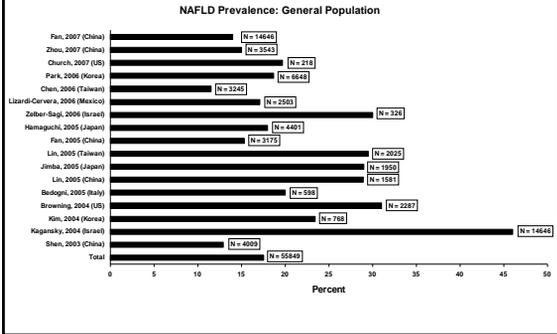
Biopsy #2:

- ~ 5 yrs later
- Steatosis
- Fibrous septa
- Cirrhosis due to NASH

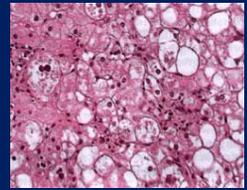
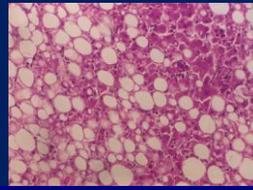
NAFLD and NASH

- Nonalcoholic fatty liver disease (NAFLD) ranges from fat deposition alone to NASH with fibrosis
 - Estimated prevalence of NAFLD in US adults: 40-60 million
 - Accounts for 50-60% of visits for abnormal LFTs
- Nonalcoholic steatohepatitis (NASH) is a subset of NAFLD
 - Steatosis with requisite inflammation and often fibrosis
 - Requires a biopsy to diagnose
 - Estimated prevalence of NASH in US adults: 9-10 million
 - 1.5-2 million of those with NASH will develop cirrhosis
 - New NASH diagnoses are rising

NAFLD – Prevalence



NAFLD vs. NASH



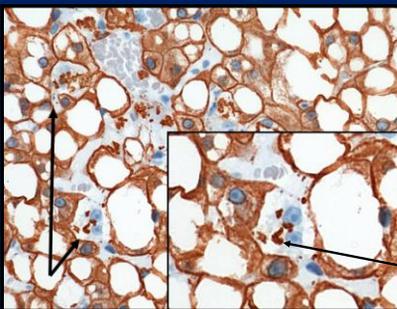
NAFLD

- Lipid droplets
- ≥ 10% of field involved
- No inflammation
- No fibrosis

NASH

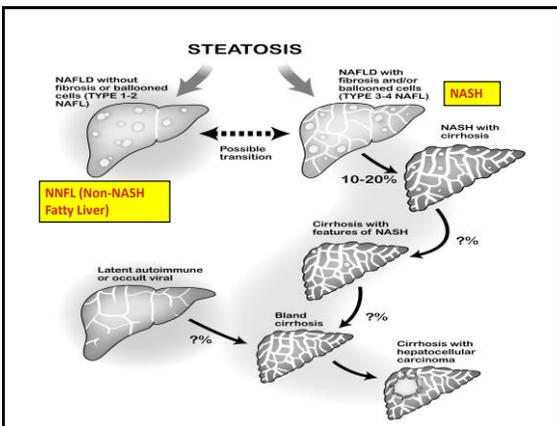
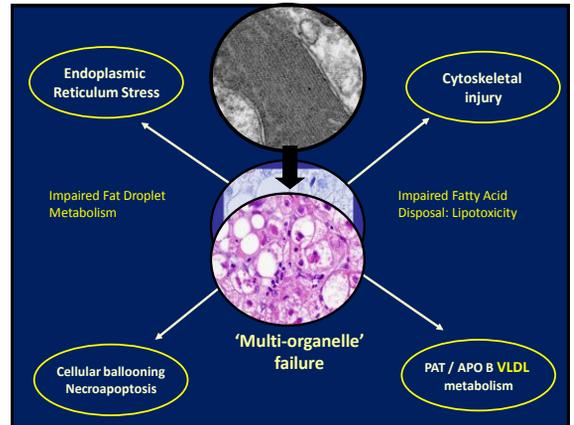
- Lipid droplets + inflammation
- Ballooned cells and periportal inflammation
- Fibrosis not required but often present

Keratin (cytoskeleton) injury is evident in ballooned cells



K8/18 staining in NASH
Lackner et al.
Hepatology 2008

Loss of keratin with Mallory Denk Body



NAFLD and Survival Outcomes

- Among Japanese patients with type 2 diabetes, the cause of death was cirrhosis in 6.4% (compared to 19.5% due to heart disease)
 - However, the ratio of observed vs. expected deaths was higher for cirrhosis than for heart disease (2.67 vs. 1.81)
- In another report, the 5- and 10- year survival in NASH cirrhotics is estimated at 67% and 59%
- In a third study with 12 years of follow-up, NASH patients had similar liver-related mortality as ambulatory ASH patients

Sasaki A et al, Diabetes Res Clin Pr 1989
Propst A et al, Gastroenterol 1995
Cortez-Pinto H et al, Dig Dis Sci 2003

NAFLD and Aminotransferases

- Aminotransferases are poor predictors of steatosis
 - Dallas Heart Study: 79% of patients with steatosis had normal LFTs
 - 1/3 of NAFLD patients with normal ALT have advanced (stage 3 or 4) fibrosis
- Marked ALT increases occur with no clinically significant hepatic injury

Browning JD. Hepatology 2004
Mofrad P. Hepatology 2003
Pfeffer MA. Circulation 2002.

NAFLD: Predictors

- Hypercholesterolemia and hypertriglyceridemia are independent predictors of steatosis
 - Steatosis in 60% of hyperlipidemic pts and 83% of those with hyperlipidemia and increased ALT
- Diabetes is also an independent predictor of steatosis

Sasaki A et al. Diabetes Res Clin Pr 1989

NAFLD and NASH: Evaluation

- Diagnosis of exclusion
 - Key exclusions
 - Alcohol – Men < 30 gm/day, Women < 20 gm/day
 - Viral hepatitis
 - Autoimmune liver disease
 - Autoimmune hepatitis: ASMA and IgG
 - Primary biliary cirrhosis (PBC): AMA and IgM
 - Primary sclerosing cholangitis: Coexistent IBD → MRCP
 - Metabolic liver disease
 - Wilson disease: ceruloplasmin
 - Hemochromatosis: ferritin, iron saturation
 - A1AT deficiency: A1AT level
- Obtain complete abdominal ultrasound

NAFLD and NASH: Evaluation

- Obtain complete abdominal ultrasound
 - Evaluate steatosis
 - Not much granularity (present or absent)
 - May miss patients with < 20% steatosis
 - Evaluate spleen size (especially important in patients with borderline or low platelet count)
 - Necessary prior to liver biopsy (if indicated)

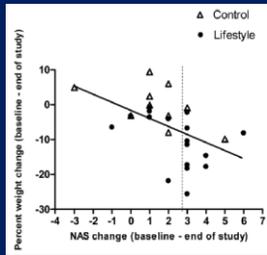
Therapy Considerations

NAFLD and Insulin Resistance (IR)

- Insulin resistance is a key component to increasing fat in the liver and occurs at multiple sites

Tissue	Dysfunction
Adipose	Failure to suppress hormone-sensitive lipase allows release of free fatty acids from triglyceride stores
Liver	Failure to suppress glucose production/release
Muscle	Failure in glucose uptake due to immobile glucose (GLUT-4) transporter, increase myocyte lipid stores, poor mitochondrial function

Weight Loss and Exercise in NAFLD



N=31
48 wks
Decrease by ≥7%

As weight goes down related to lifestyle modifications, so does NAS score

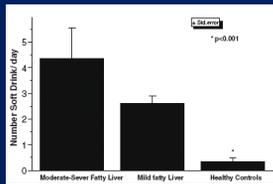
Promrat K et al. Hepatology 2010.

Weight Loss and Exercise in NAFLD

- What recommendations should I give my patient?
 - 4 weeks of moderate-to-high intensity exercise (50-70% VO₂max) for 150 min/wk:
 - Reduction in hepatic triglycerides and decrease in visceral fat
 - No change/mild increase in muscle triglyceride content
 - Exercise affects liver fat first and leads to a shift to fat as a primary fuel for skeletal muscle
 - Conclusions:
 - Moderate-intensity exercise at minimum of 150 min/week
 - More time and more intense exercise is better – watch injuries that can break the habit

Johnson NJ, Hepatology 2009

Dietary Composition



Soft-drink consumption is associated with more severe fatty liver

Abid A et al. J Hepatol 2009.

	Adjusted (Model 2)	
	OR(95%CI)	P Value
Steatosis		
Fructose consumption		
0 serving	0.7 [0.4, 1.1]	0.10
≥7 servings	0.4 [0.2, 0.9]	0.02
Histologic inflammation		
Fructose consumption		
0 serving		
0-7 servings	0.8 [0.5, 1.4]	0.53
≥7 servings	1.1 [0.6, 2.3]	0.70
Ballooning		
Fructose consumption		
0 serving		
0-7 servings	0.9 [0.5, 1.5]	0.73
≥7 servings	1.4 [0.7, 2.7]	0.32
Fibrosis		
Fructose consumption		
0 serving		
0-7 servings	0.9 [0.6, 1.5]	0.78
≥7 servings	2.4 [1.4, 5.0]	0.004

Dietary fructose is associated with worse steatosis and fibrosis

Abdelmalek MF et al. Hepatology 2010.

Antioxidants

	N	RCT or Open	Agent	Dose	Duration	ALT	Histology	Imaging
VITAMIN E								
Umetani (2005)	11	Open label	Vitamin E	400-1,200 IU	4-10 mo	Improved	Not evaluated	Not evaluated
Haugens (2001)	12	Open label	Vitamin E	300 mg	12 mo	Improved	Improved steatosis, inflammation, and fibrosis	Not evaluated
Hemibiotin (2003)								
	45	RCT	Vitamin E	1,800 IU	6 mo	Improved	Improved fibrosis (with vitamin C)	Not evaluated
Coghlan (2003)								
	14	RCT	Vitamin E	200 IU	3 mo	Improved	Not evaluated	Not evaluated
Vagin (2004)								
	28	RCT	Vitamin E	400-1,000 IU	5 mo	Improved	Not evaluated	Not evaluated
Kamada (2004)								
	10	Open label	Vitamin E	300 mg	6 mo	Improved	Not evaluated	Not evaluated
Sanyal (2004)								
	10	Open label	Vitamin E	400 IU	6 mo	Improved	MRI improved steatosis	Not evaluated

Several past RCTs of Vitamin E unfortunately did not focus on histological outcomes, so it is still somewhat difficult to fully support the widespread use of Vitamin E in NASH, especially in patients with CVD risk factors (many NASH pts obviously)

Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality

Edgar R, Miller III, MD, PhD; Roberto Pastor-Barraza, PhD; Dianshan Dalai, MD, MPH; Rudolph A. Biemens, PhD, FRCP; Lawrence J. Appel, MD, MPH; and Bruce Guallar, MD, DPH

Miller ER et al. Ann Intern Med 2005.

Insulin Sensitizers

- By far the most studied group of pharmacologic agents for NASH
- Excellent pathophysiologic underpinnings for usefulness

- **Metformin**: Works by reducing hepatic glucose production and increasing peripheral glucose utilization via enhanced glucose transport in the mitochondria of skeletal muscle

- Clearly provides direct improvement in insulin sensitivity

- **Thiazolidinediones (TZD)**: Agonists of PPAR-gamma receptor

- TZDs promote decreased central/visceral adiposity at the cost of increased peripheral adiposity (and weight gain)
- This effect in part results in improved insulin sensitivity

Treatment of NASH: TZDs

Thiazolidinediones

Author	N	Agent	Dose	Duration	Effects
Sanyal (2004)	20	Pio	30 mg	6 mo	Significant improvement in steatosis and inflammation, nonsignificant improvement in fibrosis
Belfort (2006)	55	Pio	45 mg	6 mo	Significant improvement in liver fat, ALT, steatosis, inflammation; nonsignificant improvement in fibrosis
Aithal (2008)	74	Pio	45 mg	12 mo	Significant improvement in ALT, ballooning, fibrosis; nonsignificant improvement in steatosis
Ratzl (2010)	53	Rosi	8 mg	3 yr	Significant improvement in ALT, steatosis; nonsignificant improvement in inflammation, fibrosis
Sanyal (2010)	163	Pio	30 mg	96 wk	Significant improvement in ALT, steatosis, ballooning, inflammation, NAS and fibrosis

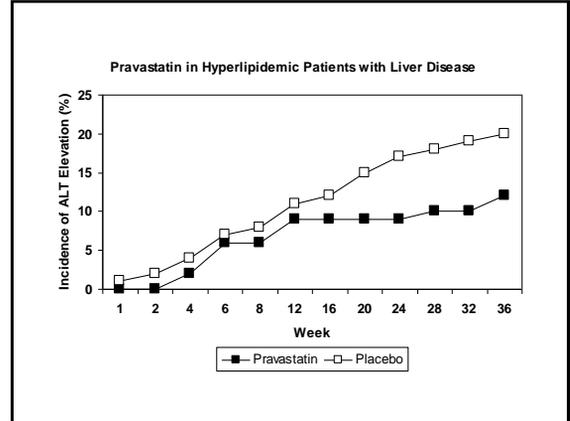
- These results are all in non-diabetic NASH patients only
- Results are not durable without lifestyle modification after D/C

Caldwell SH et al. Schiff's The Liver, 11th ed, 2011.

NAFLD and Statins

- NASH patients have higher overall mortality, predominantly due to cardiovascular disease
 - The ratio of observed vs. expected deaths, however, was higher for cirrhosis than for heart disease (2.67 vs. 1.81)
 - Estimated 5-year survival in NASH cirrhotics: **67%**
 - Statins are an important adjunct in many NAFLD patients
 - Start low and increase slowly as guided by lipids and try not to overreact to ALT elevations

Probst A et al. Gastroenterology 1995
Cortez-Pinto H et al. Dig Dis Sci 2003



Conclusions

- Exercise and weight loss are the only certain methods to slow or stop NASH progression
 - Exercise is probably more important than weight loss in comparing exercise studies with bariatric surgery
 - **Be as specific as possible about your recommendations about exercise, weight loss, and dietary modifications**
 - ≥ 150 min/wk moderately paced – minimum eventual goal
 - ≥ 7 -10% loss of current weight

Conclusions

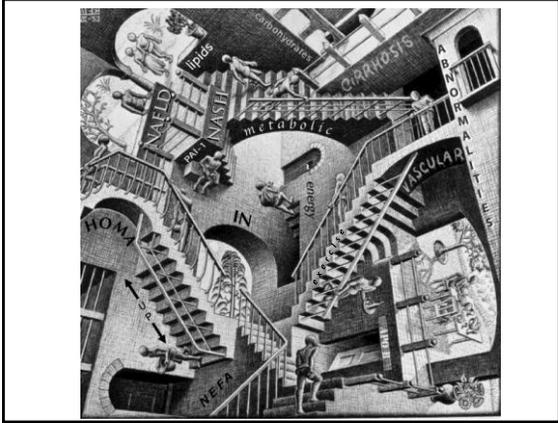
- TZDs have some beneficial effects in NASH, but they may not be enough alone to prevent fibrosis progression (and effects are not durable with discontinuation)
- Metformin may still have a role in inducing weight loss and improving insulin sensitivity, but alone probably not enough
- Vitamin E appears promising, but the possibility of harm long-term has not been fully addressed and should only be used in patients with biopsy-proven NASH
- Hypolipidemics may play a role in NASH therapy, but more likely in addressing associated medical comorbidities

NAFLD and NASH: Who to Refer

- In the setting of hepatic steatosis on US and abnormal LFTs, any of:
 - HOMA-IR > 2.5
 - $\text{HOMA-IR} = \text{fasting Glucose(mg/dl)} \times \text{fasting Insulin}(\mu\text{U/mL}) / 405$
 - ALT > 100 IU/L – not hard and fast rule
 - Persistence of elevated ALT – months to years
 - Multiple positive metabolic syndrome factors
 - New diabetes or recent worsening of control and more elevated ALT
 - Coexistent cardiovascular disease, hyperlipidemia, and difficult decision regarding statin use
 - Family history of cirrhosis not involving alcohol or viral hepatitis
 - Thrombocytopenia of unclear etiology

My Approach

- Encourage exercise and dietary modification first to induce weight loss and improve fitness/IR – 4-6 months
- If no evidence of change, then use liver biopsy selectively: patient's motivation for undergoing evaluation and making changes is key
- If NASH, then measure insulin resistance with fasting serum insulin and glucose levels to calculate insulin sensitivity (HOMA-IR)
- If insulin resistance is present, then vitamin E and metformin are usual first agents to improve insulin resistance and help reduce weight – 12 months
- **Pioglitazone only if metformin/vitamin E not effective in reversing IR – repeat measurements of HOMA-IR and weight**
- **Repeat liver biopsy in 3-4 years to assess for histologic improvement in inflamm, ballooning, and steatosis (?fibrosis)**



Thanks for your attention!

Curtis K. Argo, MD, MS

University of Virginia

cka3d@virginia.edu

