The Skinny On Non Alcoholic Fatty Liver Disease

UCSF Advances in Internal Medicine

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Non Alcoholic Fatty Liver Disease: Outline

- Pathogenesis
- Epidemiology
- Diagnosis
- Hepatology Referral?
- Management Options

Causes of Fatty Liver

Drugs and Toxins
- **ALCOHOL**
- Corticosteroids
- Tamoxifen
- Amiodarone
- Industrial solvents

Nutritional Syndromes
- JI Bypass
- TPN
- Rapid weight loss

Inherited Metabolic Diseases
- Lipodystrophy
- Abetalipoprotinemia
- Wilson's Disease

Causes of *Non Alcoholic Fatty Liver Disease (NAFLD)*

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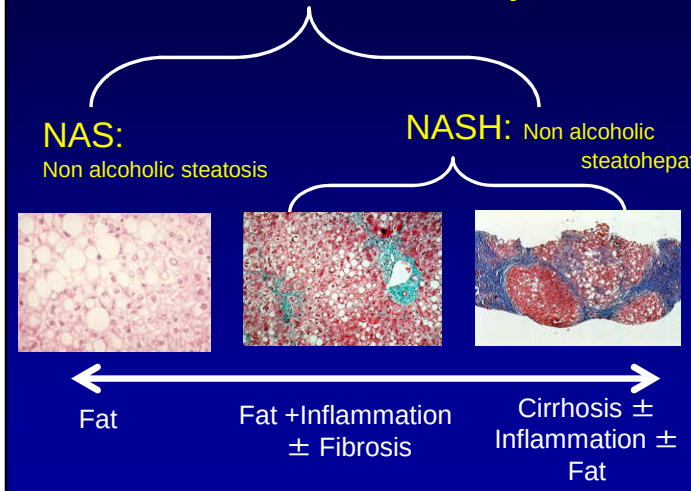
Metabolic Syndrome
- IR/DM
- Obesity
- Dyslipidemia
- Hypertension

Additional High Risk Groups

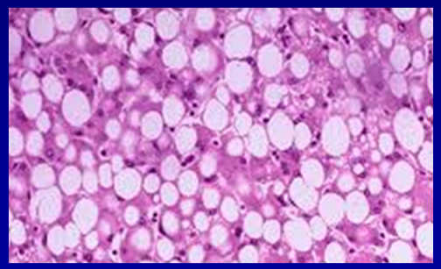
- Hypothyroidism
- Obstructive Sleep Apnea
- Hypogonadism
- Hypopituitarism
- Polycystic Ovarian Syndrome

AASLD Practice Guidelines NAFLD 2014

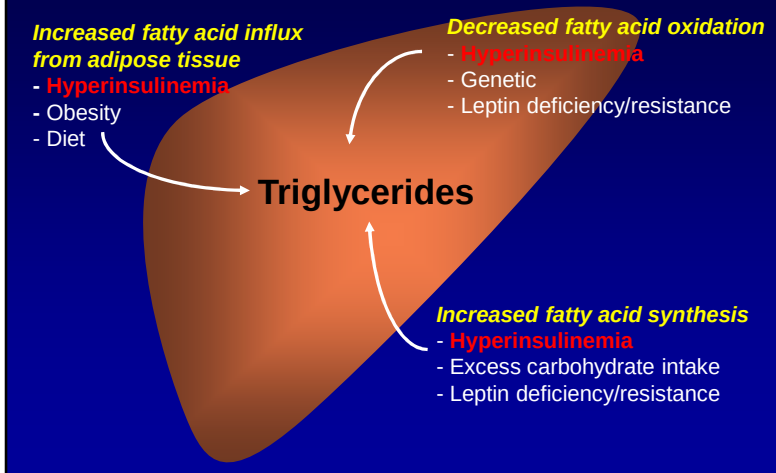
NAFLD: Non Alcoholic Fatty Liver Disease

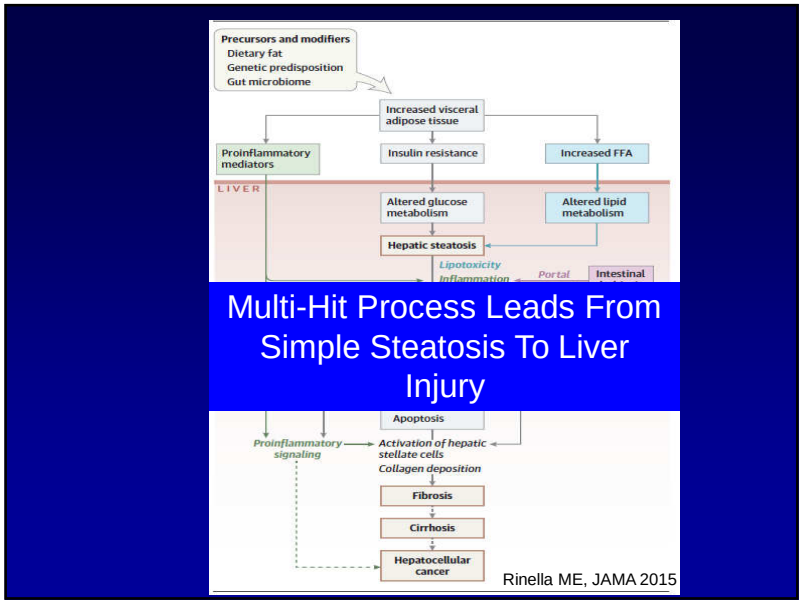


PATHOGENSIS OF STEATOSIS AND STEATOHEPATITIS

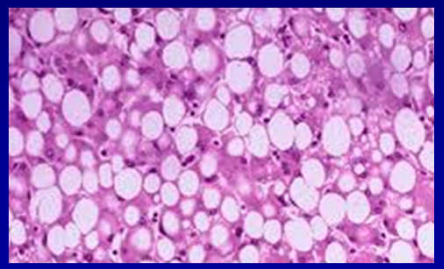


Fat Accumulation in the Liver



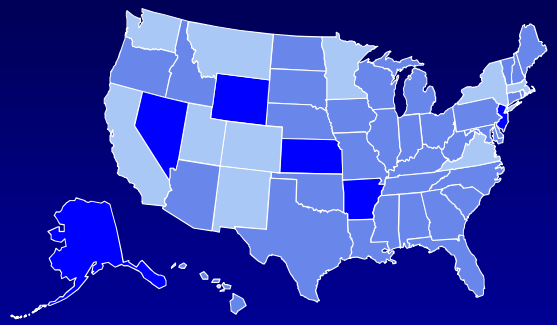


EPIDEMIOLOGY OF STEATOSIS AND STEATOHEPATITIS



Obesity Trends Among U.S. Adults

1990

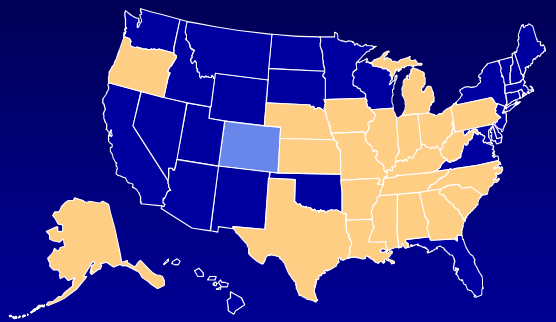


BMI ≥30, or ~ 30 lbs. overweight for 5′ 4″ person

No Data | <10% | 10%–14%

Obesity Trends Among U.S. Adults

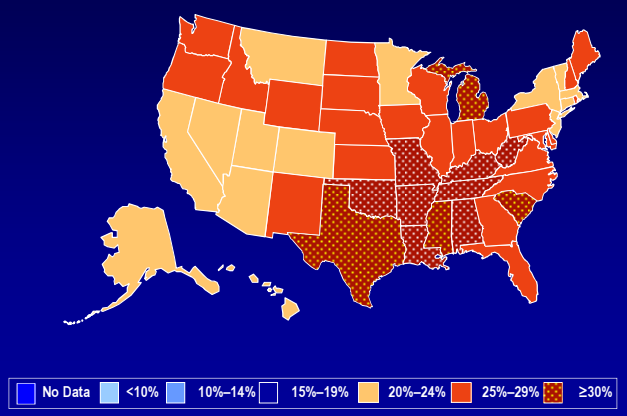
2000



No Data | <10% | 10%–14% | 15%–19% | ≥20%

Obesity Trends Among U.S. Adults

2010



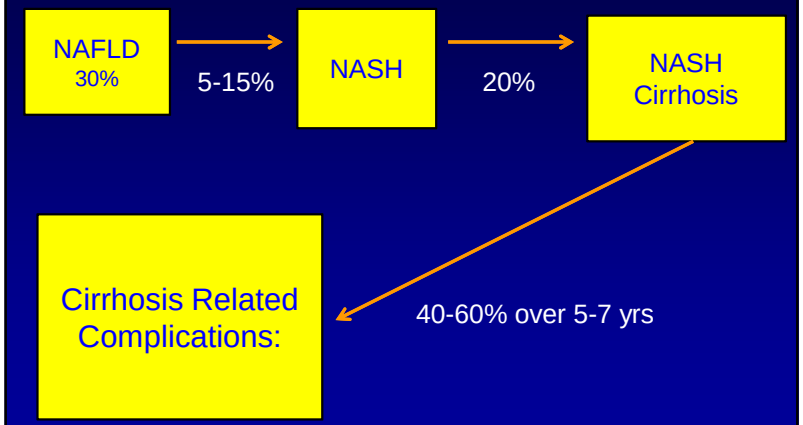
Epidemiology

- What is the prevalence of NAFLD in general population?
  30%
- Prevalence of NAFLD in morbid obesity?
  80-90%
- Prevalence of NAFLD in DM2?
  70%
- Prevalence of NAFLD in hyperlipidemia?
  50%

NAFLD = Hepatic Manifestation of the Metabolic Syndrome

Chalasani et al., Am J Gastro 2012

Natural History

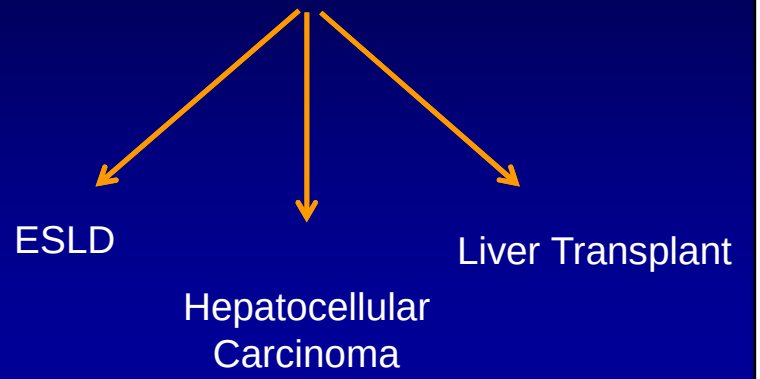


Rinella ME, JAMA 2015

Implications of NAFLD:

Within the next 8-10 years

NASH Cirrhosis



Charlton et al., Gastro 2011

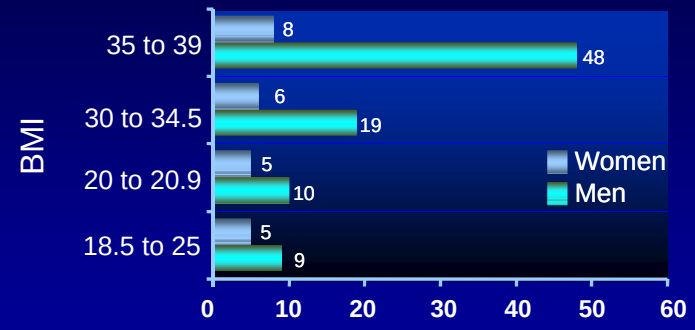
Hepatocellular Carcinoma Risk in NASH

HCC Risk in NASH

- 50% of HCC develops in absence of cirrhosis
- Inflammatory processes related to steatohepatitis appear to promote cancer growth
- Decreased activity of p53 tumor suppression genes
- Diabetes and Obesity are INDEPENDENT risk factors for HCC

Rinella ME, JAMA 2015; El-Serag et al, Gastro 2004; Starley et al, Hepatology 2010.

Obesity and HCC-related Mortality

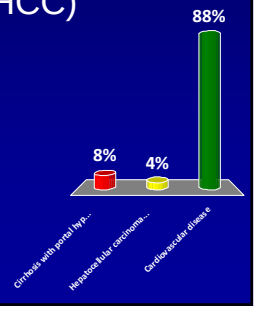


- N= 900,000 cancer free at enrollment
- Followed for 16 yrs
- N= 57,145 new cancers

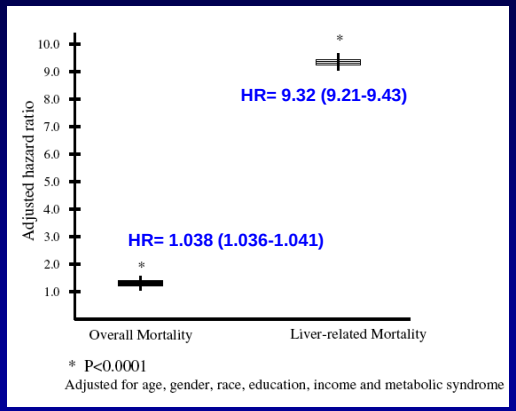
Calle et al, NEJM 2003

1) What is the most common cause of death in patients with NAFLD?

A. Cirrhosis with portal hypertensive complications
B. Hepatocellular carcinoma (HCC)
C. Cardiovascular disease



Mortality in NAFLD



- NHANES III
- Eligible: 12,822 (817 NAFLD)
- F/U: 8.7 yrs (median)

Causes of death in NAFLD:

1) **CV**
2) Malignancy
3) Liver

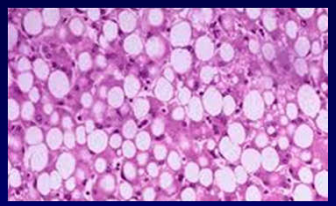
Ong et al. J Hepatology 2008

Independent Risk Factors for Clinically Significant CAD

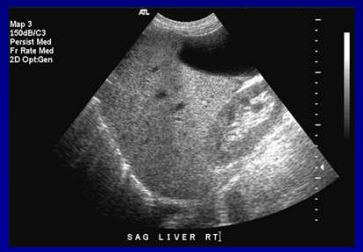
- N=317 elective coronary angiogram
- N=85 Normal or mild CAD and N=232 Clinically relevant CAD

Variable	OR	95% CI	P Value
Fatty Liver	8.48	4.39-16.40	<0.001
Diabetes	2.54	1.47-5.91	0.002
Male Sex	2.31	1.19-4.48	0.014
HTN	1.63	0.90-2.98	0.106
LDL	0.99	0.99-1.00	0.201

Mirbagheri et al. Liver Internat. 2007



NAFLD DIAGNOSIS



Diagnosis of Non-Alcoholic Fatty Liver Disease

Abdominal imaging with steatosis (+/- elevated liver enzymes)

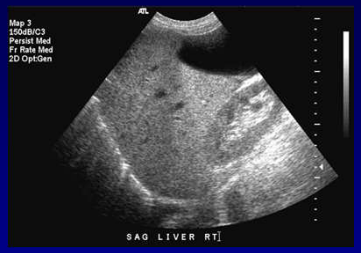
+

Other causes of CLD excluded

+

Usually with clinical evidence of metabolic syndrome

Detecting the Presence of Steatosis

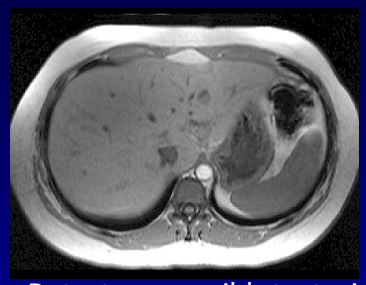


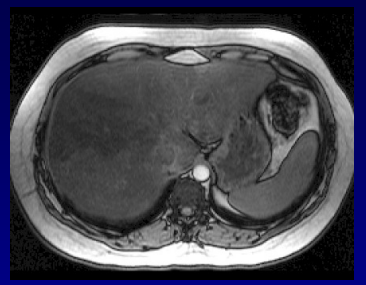
- Bright liver
- Echotexture - increased compared to kidney

Advantages:
- Widely available
- Inexpensive
- Painless

Limitations:
- Lacks sensitivity
  - Requires 30% steatosis

Steatosis on MRI





- Detects even mild steatosis
- Evolving technology with improved sensitivity: ie MR spectroscopy, Proton-Density Fat-Fraction (PDFF)
- Good research tool for longitudinal studies of steatosis

Rinella et al. *Liver transplantation* 2003

Incidentally Detected Steatosis By Imaging in Primary Care Setting:

1) Exclude alcohol and culprit meds (heavy alcohol: > 21 drinks in men or > 14 drinks in women weekly)
2) Evaluate for Metabolic Syndrome: DM, HTN, obesity, HL
3) Perform liver tests: bilirubin, AST, ALT, alk phos

Elevated Live… (check HBV/H…

Tests

20% of NAFLD patients with normal liver enzymes have hepatic fibrosis

Hepatology Referral

What would a hepatologist order?

Guided by history, presentation, and pattern of injury, not shotgun approach:

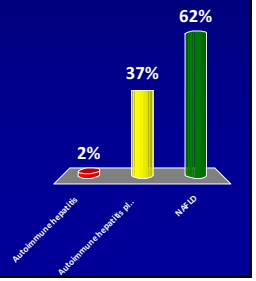
- AMA, IgM (for PBC)
- ASMA, ANA, IgG
- A1AT phenotype
- Iron, Tsat, ferritin
- HAV Ab (for vaccination)
- HBsAg, sAb, cAb
- HCV Ab
- Ceruloplasmin age < 45
- HgAIC
- Fasting lipids

Question

2) 54 y/o M with diabetes, hyperlipidemia, HTN and morbid obesity. Ultrasound notes diffuse fatty infiltration. ALT 50, AST 45. ANA >1:160 and ASMA 1:40.

What is *most likely* cause of abnormal liver tests?

A. Autoimmune hepatitis
B. Autoimmune hepatitis plus NAFLD
C. NAFLD



Autoantibodies in NAFLD

- Positive ANA > 1:160 or ASMA >1:40 were present in 21% of patients with NAFLD
- Positive AMA can be seen in 8% patients with NAFLD
- Autoimmune markers are not associated with more advanced histology

Vuppalanchi R et al., Hepatol Int 2011

When to Biopsy?

- To exclude other types of liver disease
- If atypical phenotype: NAFLD in absence of metabolic risk factors
- To confirm stage of fibrosis in those at increased risk for advanced disease: age > 45, DM, obesity, AST/ALT> 1, ALT > 3-5x ULN
- To diagnose NASH prior to pharmacotherapy
- To support major therapeutic decision – ie bariatric surgery, clinical trials

Limitations of Liver Biopsy

- Underestimating fibrosis
- Inter and intra-observer variability
- Limited measurements

Non invasive measures of fibrosis…..

Colloredo G, J Hepatol 2003; Bacchetti P, BMC Infect Dis 2007; Brunetti E, J Hepatol 2004

NAFLD Fibrosis Scoring Systems

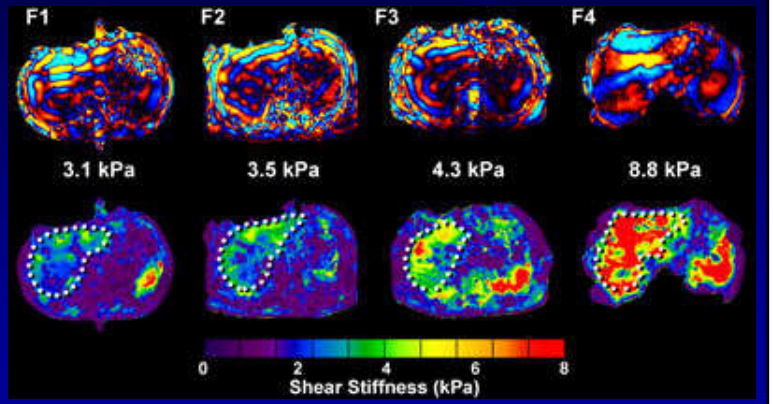
Table 1 | Predicting advanced fibrosis (F3–4) using routine clinical and laboratory variables in patients with NAFLD

Predictive score	Patients (*n*)	Variables/formula [units]	AUROC (95% CI)	Cut-off points	PPV (%)	NPV (%)
NAFLD fibrosis score[82]	733	−1.675+0.037×age [years]+0.094×BMI [kg/m²] +1.13×IFG/diabetes [yes = 1, no = 0] +0.99×AST:ALT ratio−0.013×platelet count [×10⁹/l]−0.66×albumin [g/dl]	0.88 (0.85–0.92)	≤−1.455 ≥0.676	56 90	93 85
BARD score[84]	827					96
FIB-4 score[90]	541	×√ALT [U/l])	(0.76–0.85)	≥2.67	80	90 83
FibroMeter™ NAFLD[89]*	235	0.4184 glucose [mmol/l]+0.0701 AST [U/l] +0.00008 ferritin [µg/l]−0.0102 platelet [g/l] −0.0260 ALT [U/l]+0.0459 body weight [kg] +0.0842 age [years]+11.6226	0.94	≤0.611 ≥0.715	NA 90	90 NA
Hepascore[88]‡	242	Exp −4.185818−(0.0249 age [years])+(0.7464 sex [male sex = 1; female sex = 0])+(1.0039 α2-macroglobulin [g/l])+(0.0302 hyaluronic acid [µg/l]) +(0.0691 bilirubin [µmol/l])−(0.0012 GGT [U/l])	0.814 (0.73–0.90)	0.37	57.1	92.4

Limited Discrimination Between Intermediate Stages of Fibrosis

Castera et al., Nat Rev Gastroenterol Hepatol 2013

Magnetic Resonance Elastography



Courtesy of The Mayo Clinic

Transient Elastography (Fibroscan®)

- FDA approved in 2013 for staging liver fibrosis
- US-based probe transmits vibrations through liver: velocity correlates with degree of scarring
- Validated for all stages of NAFLD related scarring
- Painless, quick, performed at bedside
- XL probe facilitates use in obese patients

SCREENING FOR NAFLD

AASLD Says:

- Patients with components of metabolic syndrome: Insufficient data to support
- Family members of NAFLD patient: No data to support

I recommend:

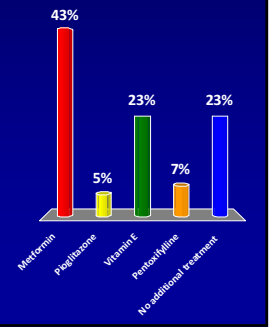
- Patients with metabolic syndrome: Yes- particularly those with obesity and diabetes
- Family members of NAFLD patient: No data to support

TREATMENT

Question

3) 55 yo man with fatty liver and obesity, but no diabetes.
Liver biopsy consistent with steatohepatitis and stage 2 fibrosis. Besides lifestyle modification what medical therapy is recommended?

A. Metformin
B. Pioglitazone
C. Vitamin E
D. Pentoxifylline
E. No additional treatment



Lifestyle Modification Exercise:

- **Moderate intensity aerobic activity 3-6 times per week for 1-3 months → no weight change but:**
  - **Improved AST/ALT**
  - **Decreases hepatic fat on imaging**
  - **No data on histologic benefits**
  - ***Long term maintenance difficult***

Thoma C et al., J Hepatol 2012, Review

Dietary Modification

- **Ideal NAFLD diet not clear: Mediterranean, Paleo?**
- **Saturated fat and fructose stimulate hepatic lipid deposition – consistently shown in animal models and humans**
- **Low-mod fat restriction with mod-high carb restriction for 1-6 months → 4-14% decreased weight**
- **Associated with improved AST/ALT, less insulin resistance, less fat on imaging, limited histology data**

Thoma C et al., J Hepatol 2012 (Review)

The Whole Package: Diet, Exercise, Behavioral Modification

- 31 obese pts, randomized 2:1 in Lifestyle (LS) vs Structured Education (controls) for 48 wks
- LS lost 9.3% versus 0.2% in controls, p= 0.003
- More pts in LS group had reduced NAS ≥ 3 points or posttreatment NAS ≤ 2 (72% vs 30%, p = 0.03)
- Greater NAS improvement in LS group (4.4 to 2.0) compared to controls (from 4.9 to 3.5) , p= 0.05
- Weight reduction correlated with improved NAS score (r = 0.497, p = 0.007)
- Weight loss of ≥7% associated with improved steatosis lobular inflammation, ballooning injury and NAS score (all p values <0.05)

Pomrat et al., Hepatology 2010

Bariatric Surgery

- **Criteria:**
  - **BMI ≥ 40 kg/m^2**
  - **BMI 35-40 kg/m^2 with significant comorbidities (DM, sleep apnea, HTN)**
  - **Failed other medically-managed weight loss programs**
  - ***15,000,000 adults in U.S. meet criteria***
- **Efficacy:**
  - **60-70% weight loss (60-250+ lbs/1-2yrs)**
  - **Best medical regimens achieve 10-25 lb weight loss**

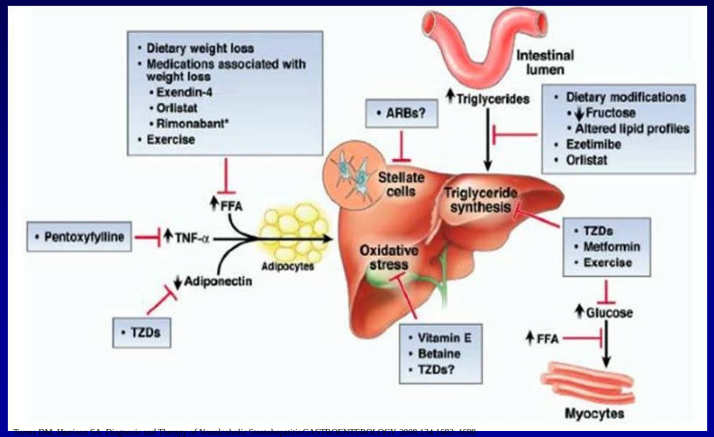
Bariatric Surgery & NASH
Caveats

- **Operative morbidity/mortality**
- **Malnutrition**
- **Rapid weight loss**
  - **Increased liver enzymes**
  - **Worsening portal inflammation & fibrosis**
  - **Acute/subacute liver failure**

Good option in select candidates with advanced fibrosis at UCSF after hepatology evaluation

MEDICATIONS

Targeting Treatment for NASH



PIVENS Trial: Pioglitzazone, Vitamin E, or Placebo for Non Alcoholic Steatohepatitis

- RTC: Adults with biopsy proven NASH

- Excluded DM and cirrhosis

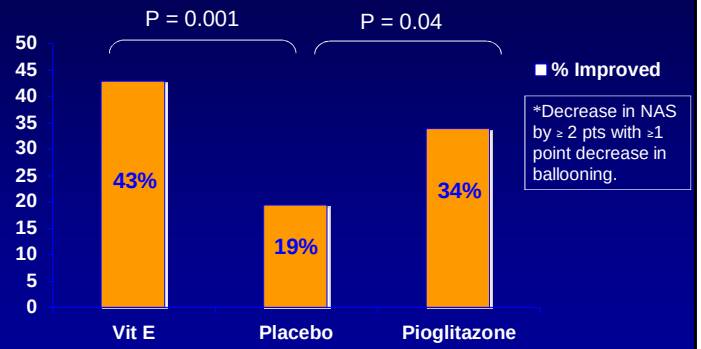
- Randomized to pioglitazone (n=80), Vitamin E (n=84), or placebo (n=83) for 2 years

- 1° endpoint = Improved composite histologic score
- 2° endpoints = Improved histologic components, anthropomorphic measures, lipids

Sanyal et al, NEJM 2010

PIVENS

Histologic Improvement in NASH*



Sanyal et al, NEJM 2010

PIVENS

Conclusions

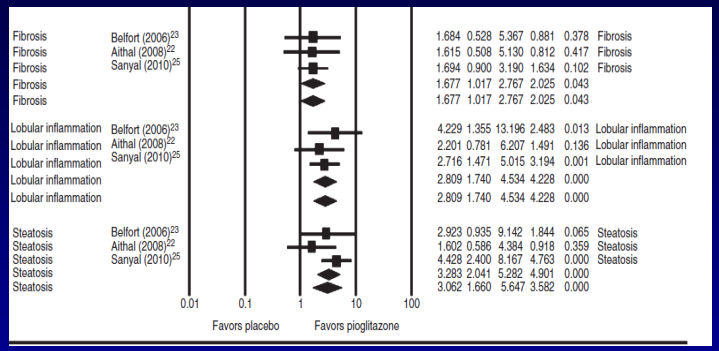
- Vitamin E superior to placebo for treatment of NASH in adult, non-diabetic patients

- Pioglitazone
  - Did not meet primary endpoint (likely due to disproportionate number with ballooned hepatocytes in treatment group)
  - Superior to placebo in improving other key histological features and liver enzymes
  - Resulted in weight gain

- Neither drug improved fibrosis score over duration of study

Sanyal et al, NEJM 2010

Pioglitazone in NASH



- Side effect profile may limit use
  - CV events, CHF, weight gain 3-5kg in 70% pts, bladder cancer?, bone fractures in post menopausal women
- Longterm safety and efficacy in NASH unknown

Aliment Pharmacol Ther. 2012

Empiric Vitamin E for Suspected NASH?

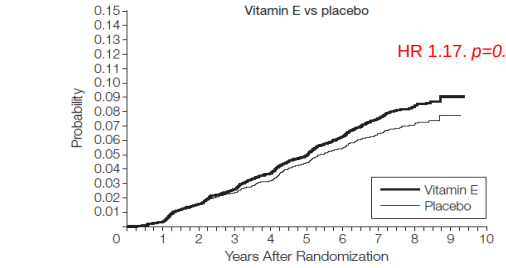
- **70-75% have isolated hepatic steatosis**
- **50% of patients don't respond to Vitamin E**
- **Increased risk for hemorrhagic stroke (RR 1.22 (95% CI 1.00-1.48)**
- **Prostate cancer risk…?**

1.Schurks et al. BMJ 2010; 2. Klein et al. JAMA 2011

Vitamin E and the Risk of Prostate Cancer

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Figure 2. Cumulative Incidence of Prostate Cancer



No. at risk

Placebo	8565	8344	8081	7831	7471	6399	4044	1833	70
Cumulative cases	32	127	201	268	367	446	503	524	529
Vitamin E	8620	8397	8150	7839	7442	6394	4010	1821	50
Cumulative cases	29	135	223	314	415	512	586	614	620

Klein et al. JAMA 2011

Pentoxifylline Improves Nonalcoholic Steatohepatitis: A Randomized Placebo-Controlled Trial

Claudia O. Zein,[1,2,3] Lisa M. Yerian,[1] Prema Gogate,[2] Rocio Lopez,[1] John P. Kirwan,[1] Ariel E. Feldstein,[1] and Arthur J. McCullough[1,3]

	Pentoxifylline N=26	Placebo N=29	P-value
NAS decrease of >2 points (ITT)	10 (38.5%)	4 (13.5%)	0.036
Steatosis	15 (75%)	5 (19%)	<0.001
Lobular inflammation	11 (55%)	6 (23%)	0.026
Ballooning	6 (30%)	6 (23%)	0.60
Fibrosis	7 (35%)	4 (15%)	0.17
Mean change in fibrosis score	- 0.2	+0.4	0.038

Zein et al. Hepatology 2012

The FLINT trial

NASH CRN

- Obeticholic acid (OCA) = potent activator of farnesoid X nuclear receptor ➔ reduces liver fat and fibrosis in animal models of NAFLD
- N = 283 patients randomized at 8 centers to OCA 25mg daily vs placebo
- 72 weeks of treatment
- Primary endpoint = Improvement in NAFLD activity score ≥ 2 + no worsening of fibrosis

Neuschwander-Tetri et al. Lancet 2015

FLINT summary

NASH CRN

- OCA significantly improved all histological features of NASH
- OCA was associated with pruritus in 23%
- OCA was associated with elevated total and LDL cholesterol and decreased HDL cholesterol
- Long term safety data needed

Neuschwander-Tetri et al. Lancet 2015

Available Therapeutic Options

- **Vitamin E: FIRSTLINE**
  - **NASH without diabetes**
  - **Insufficient evidence to treat diabetics or cirrhotics**
- **Pioglitazone**
  - **NASH with or without diabetes**
  - **Limited data in cirrhotics**
- **Pentoxifylline**
  - **Promising**
  - **Need more data on ideal subpopulation**
- **Other: Orlistat, Metformin, Statins, Fish Oil- not routinely recommended for NAFLD but certainly advise aggressive management of metabolic syndrome**

Limitations of Available Drugs

- **Effect size in all of these trials is small**
- **High placebo response rate**
- **No end point for stopping meds**

NAFLD Summary (I)

- NAFLD is most common cause of CLD- 75-100M individuals in the U.S
- NASH will soon be the leading cause of cirrhosis, HCC, and need for LT
- For incidentally detected steatosis: perform liver tests and screen for metabolic syndrome
- Patients with NAFLD should be evaluated by hepatologist

NAFLD Summary (II)

- #1 cause of death in NAFLD = CAD
- Aggressive management of cardiovascular risk factors is essential
- Steatosis is diagnosed by imaging, though diagnosis of NASH requires biopsy

NAFLD Summary (III)

- Lifestyle modification remains cornerstone: Goal weight loss 5-10% of body weight
- Vitamin E is first-line for biopsy confirmed NASH
- To date no medical therapy for NASH cirrhosis…
- Anti-fibrotic trials underway: goal to halt and reverse hepatic fibrosis

Thank You!