Alcoholic liver disease
Non-alcoholic fatty liver disease
Non-alcoholic steatohepatitis

Shivang Mehta, MD

Shivang.Mehta@bannerhealth.com

Internal Medicine Residency

Objectives

Alcoholic Liver Disease

Worldwide, ethanol accounts for…

- 3.3 million, or 5.9% of all global deaths, 5.1% of the global burden of disease
- 493,000 deaths annually are attributable to ALD
  - 47.9% of all cirrhotic deaths
  - ALD-associated liver cancer: 80,600 deaths

Based on WHO Report:

Rehm J et al. Global burden of alcoholic liver diseases. J. Hepatol 2013; 59: 160-168

Epidemiology

- Alcohol is a factor in 50% of end-stage liver disease, leading cause of liver transplant today
- 12th leading cause of death; 30,000 deaths/yr
- Cirrhosis develops in only a small percentage of drinkers
- Cirrhosis risk increases proportionally with consumption
- Mortality from EtOH cirrhosis
  - Higher than for other etiologies
  - 5 year survival: 20%

Alcohol as a Toxin

- Course depends on environmental, individually acquired and inherent modifying factors
- “Threshold Amount”: 10-12 years with doses of 40-80g/day (males) and 20-40 g/day (females)
- No particular amount will predictably cause liver disease
  - 90-100% develop fatty liver
  - 10-35% alcoholic hepatitis
  - 8-20 % develop cirrhosis
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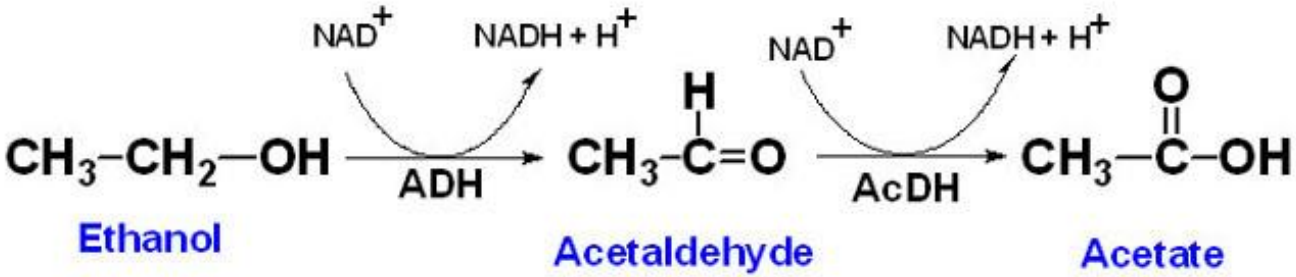
Altamirano et. al. Nat Rev Gastroenterol Hepatol. 2011 Aug; 8(9):491-501

Alcohol Metabolism



Acetaldehyde is reactive and toxic

- Forms DNA and protein adducts
- Glutathione depletion, lipid peroxidation, mitochondrial damage

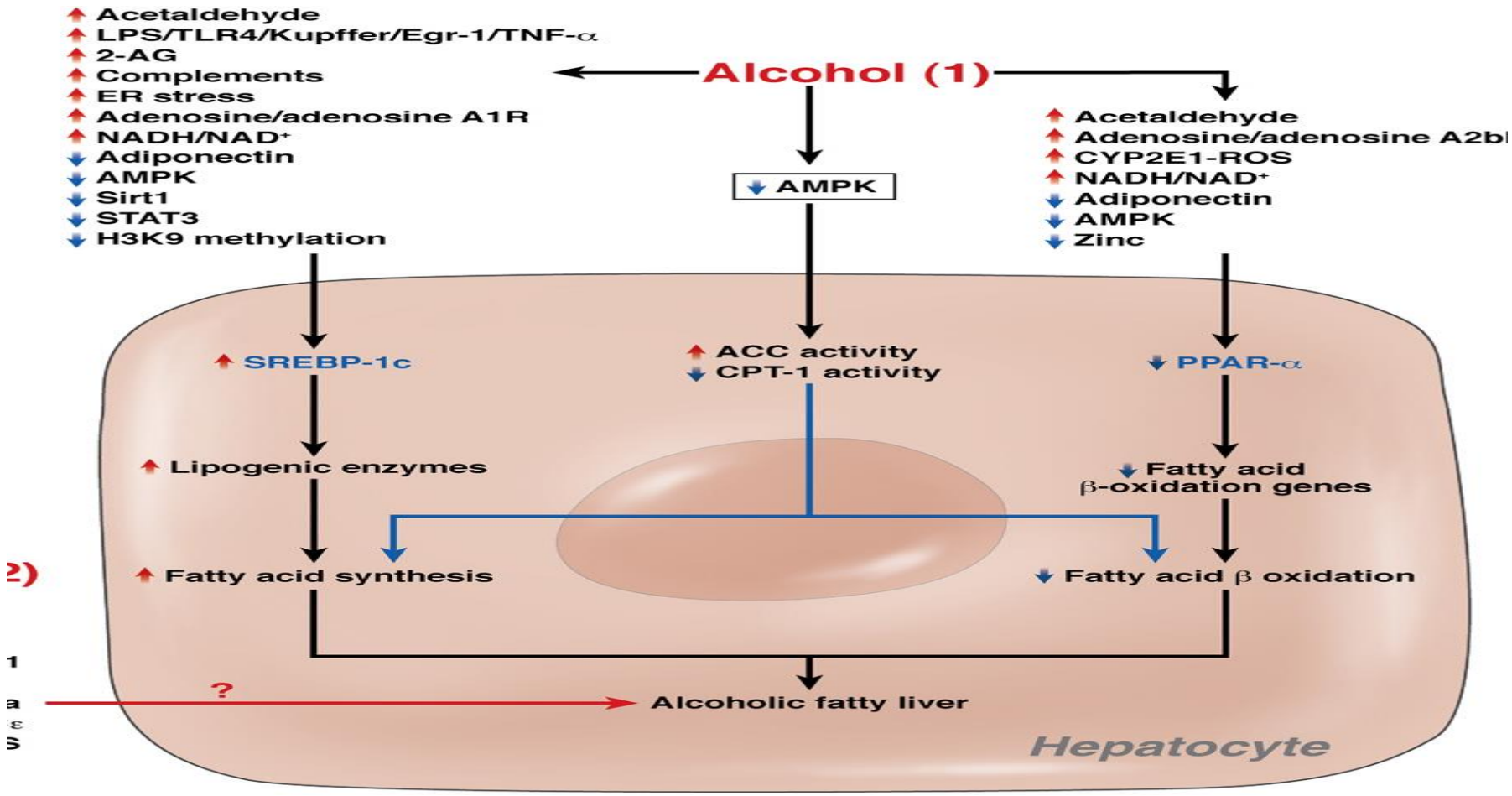
Increased NADH/NAD ratio affects carbohydrate and lipid metabolism→promotes fatty acid synthesis

O' Shea et. al. Hepatology. 2010 Jan; 51(1):307-328

Oxidative Stress

- Reactive oxygen intermediates damage tissue
- Superoxide (O_2) generated from NADPH oxidase and electron leakage from CYP2E1
  - Modifies molecules
  - Interferes with normal cellular signaling
- Ethanol leads to mobilization of free iron and generation of reactive oxygen species
- Chronic alcohol abusers have decreased antioxidant defenses

Alcohol and Fat



Modified from Gao et. al. Gastroenterology. 2011 Nov;141(5):1472-1585

Alcohol and Genetics

- Evidence for genetic contribution
  - Women are more susceptible to liver disease
  - Hispanic populations > African American & Caucasian
  - Twin Studies: Monozygotic:Dizygotic 3:1

- Genetics of Alcoholism
  - Overall heritability of alcoholism is 50%
  - Mutations in genes for GABA receptor may be linked

Li et. al. Nat Rev Genet. 2009 Apr;10(4):225-231

Environmental Modulators of Alcoholic Liver Disease

- Undisputed risk factors for disease progression
  - Obesity
  - Female gender
  - Smoking
  - Synergistic effects with
    - Hepatitis B
    - Hepatitis C
    - HIV
  - Medications

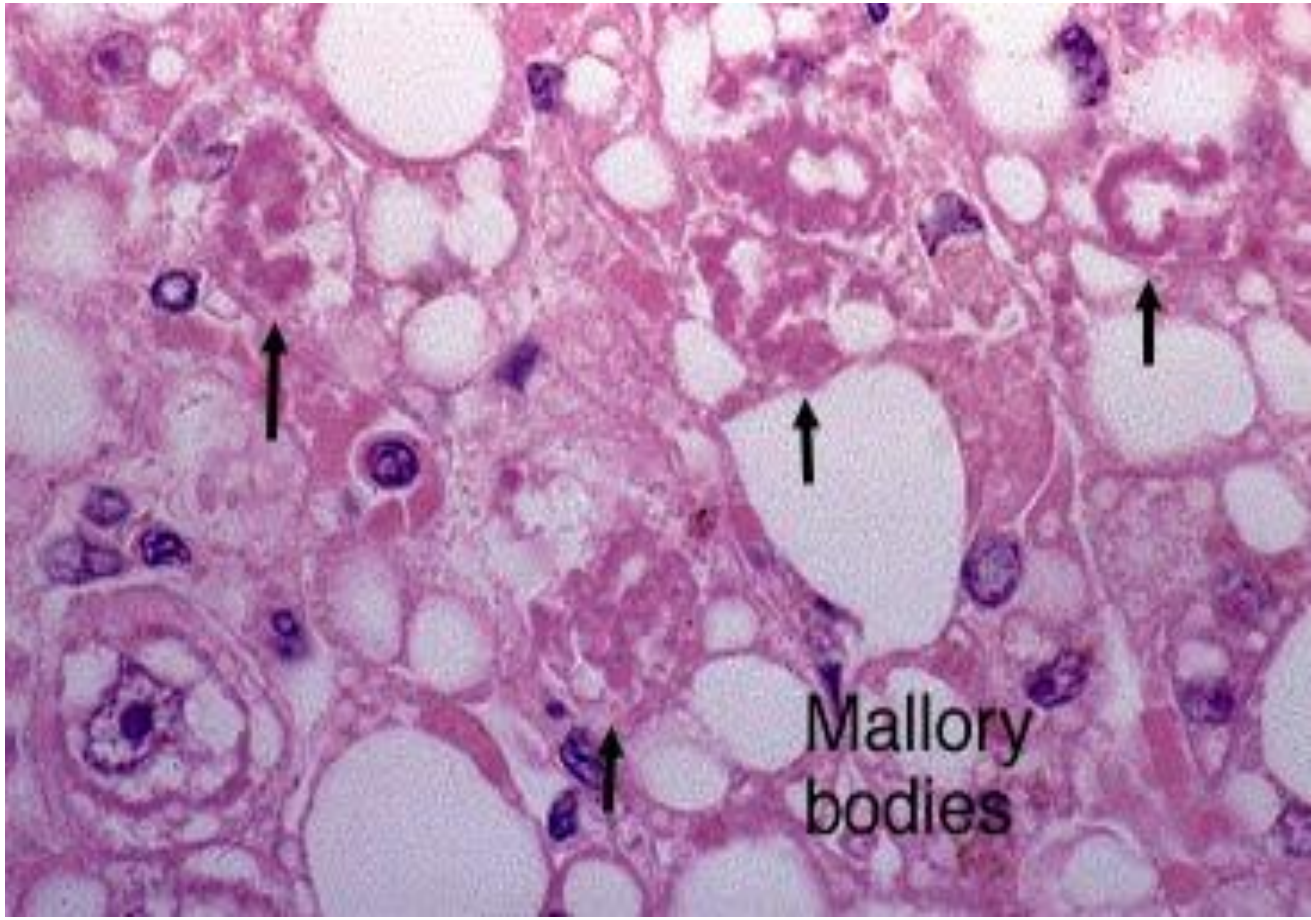
Alcoholic Hepatitis

- Clinical syndrome of jaundice and liver dysfunction generally occurring after decades
- Typical age: 40-60 yrs; female gender is a risk factor
- Cardinal signs are jaundice and hepatomegaly
- Encephalopathy and portal hypertension may be present

Louver et. al. Gastroenterology. 2009 Aug;137(2):541-548

Alcoholic Hepatitis

- Ballooned hepatocytes
- Mallory-Denk Bodies
- Intrasinusoidal and perivenular fibrosis may be present



Scoring Systems for Severity and Guiding Treatment

- Maddrey's Discriminant Function
  - DF=4.6 X [Patient Prothrombin Time—Control Prothrombin Time] + Bilirubin
  - DF > 32 threshold for consideration of treatment
- Glasgow Alcoholic Hepatitis Score
  - Includes: age, WBC, BUN, bilirubin and INR
  - GAHS > 9 threshold for consideration of treatment
- Model for End Stage Liver Disease
- Lille Score
  - Response of bilirubin after 7 days of treatment
  - Score greater than 0.45 indicates a lack of response to corticosteroids and predicts a 6-month survival rate of less than 25%

Singal et. al. Gastroenterol Clin North Am. 2011 Sep;40(3):611-639

Louvet et. al. Hepatology. 2007 Jun;45(6):1348-1354

Treatment of Alcoholic Hepatitis

- Abstinence

- Nutrition
  - VA Cooperative Studies
    - Virtually every patient with EtOH hepatitis has malnutrition
    - Patients who voluntarily consumed 3000 kcal/day had no mortality compared with 80% mortality (1000kcal/day)
    - Degree of malnutrition correlated with serious complications (encephalopathy, ascites, and hepatorenal syndrome)

- RCT of enteral tube feeding (2000kcal/day) vs. corticosteroid for 28 days: survival at 1 year similar; however, recent study showed no difference between enteral tube feeding and PO nutrition

Mendenhall et. al. JPEN. 1995 Jul-Aug;19(4):258-269

Pharmacotherapy for Alcoholic Hepatitis

- Corticosteroids
  - Decrease immune response and proinflammatory cytokines
  - Meta-analysis supports use when DF > 32; improved 1 month mortality but not beyond 1 year
  - Limited applicability given frequency of infection

- Pentoxifyline
  - Phosphodiesterase inhibitor; modulates TNF-α
  - Prevention of hepatorenal syndrome

- STOPAH trial revealed that neither agent is very effective with corticosteroids improving 30 day mortality in post hoc analysis

Therapy That Doesn’t Work

- Propylthiouracil
  - Reduce hypermetabolic state, antioxidant
  - Recent Cochrane Review (700 patients): negative
- Colchicine
  - Anti-fibrotic agent
  - VA Cooperative study showed no benefit
- Anti-TNFα Agents
  - Small clinical trials with infliximab and etanercept
  - Mostly negative, some stopped prematurely

Sharma P et. al. J Hepatol. 2009 Mar;50(3):584-591

Liver Transplant for Alcoholic Hepatitis

- 6 months of abstinence usually required
- Non-responders to medical therapy have a 6 month survival of 30%, majority of deaths in first 2 months
- Highly selective French study evaluated early liver transplantation→improved survival
- Highly controversial practice

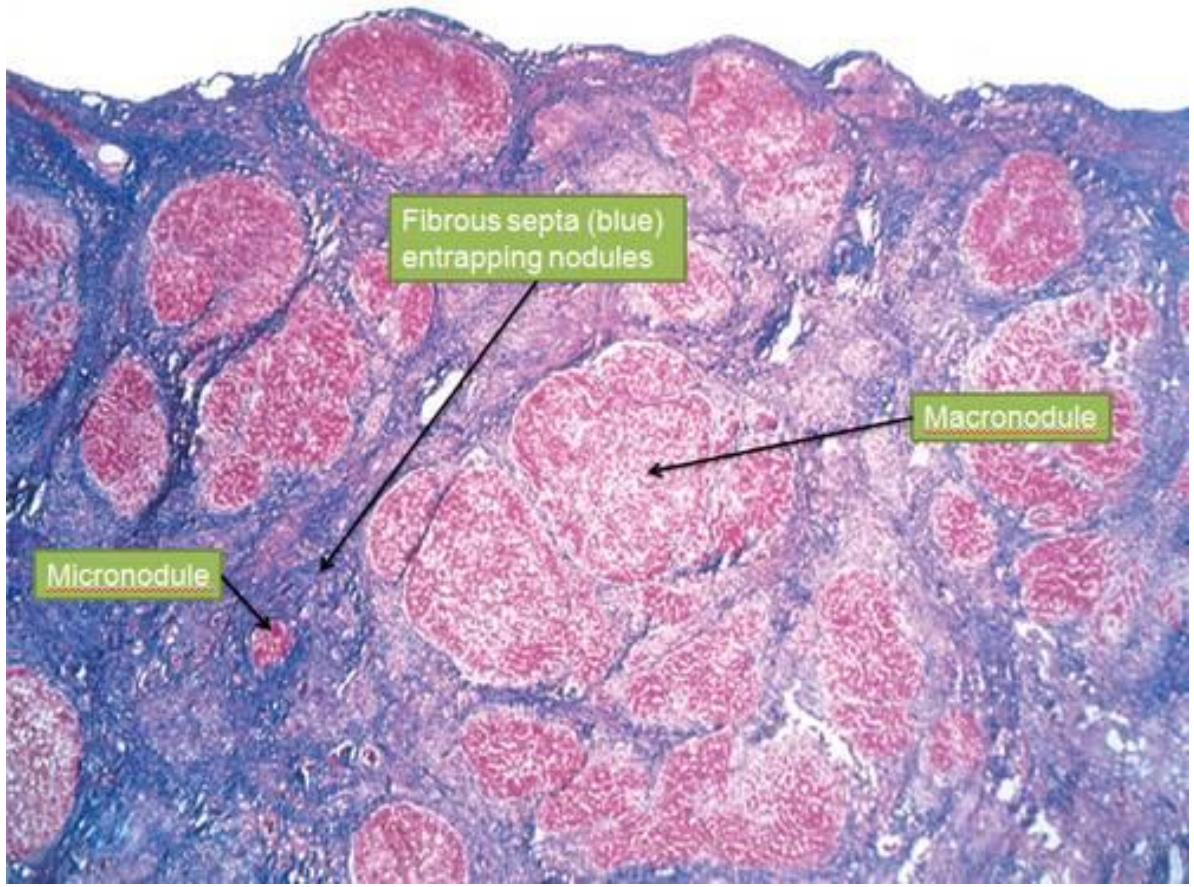
Mathurin P et. al. N Engl J Med. 2011 Nov;365(19):1790-1800

Alcoholic Cirrhosis

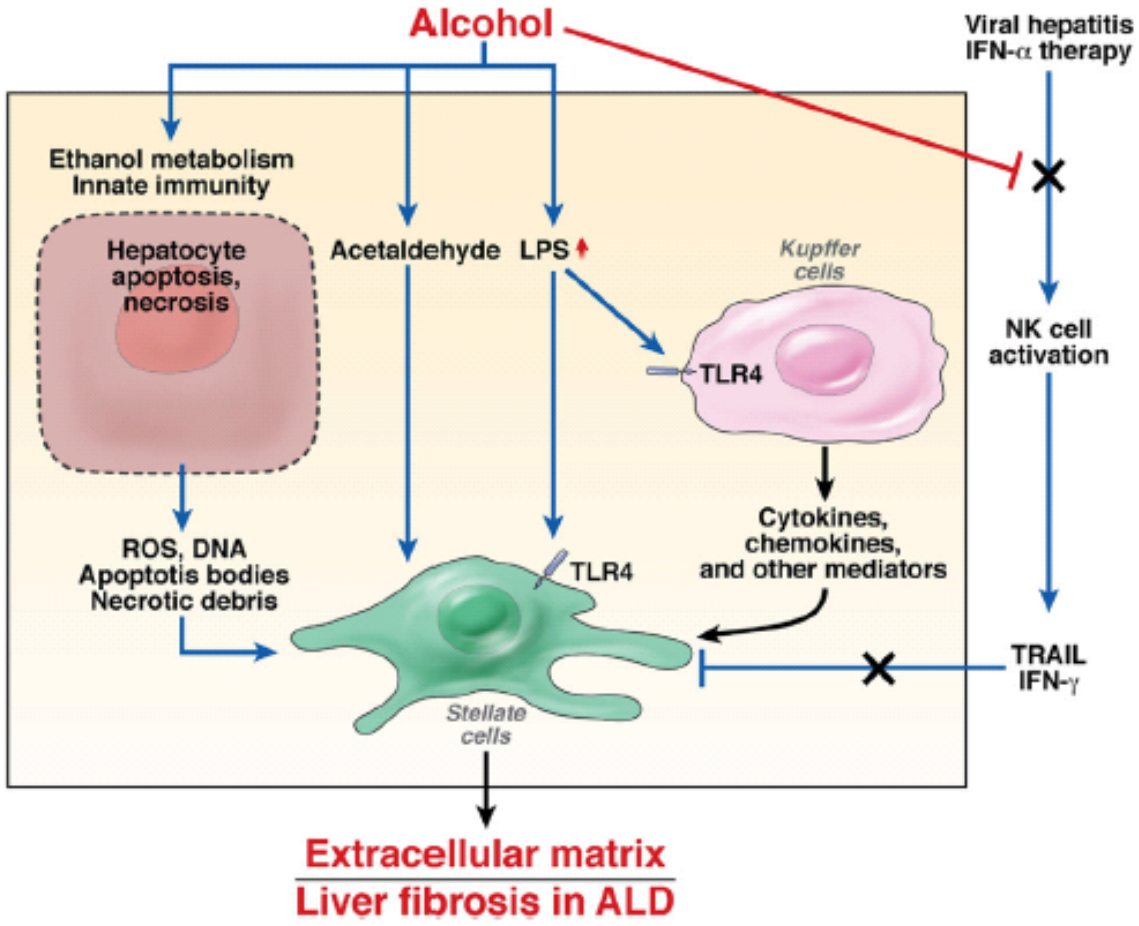
- Only 20% of heavy drinkers
- Presence or absence of symptoms largely due to presence or absence of decompensation
- Once cirrhosis established 1-2% annual risk for hepatocellular carcinoma

Alcoholic Cirrhosis

- Traditionally classified as micronodular cirrhosis but often mixed
- Earliest collagen deposition around terminal venules
- EtOH hepatitis changes may be superimposed



Mechanisms of Fibrosis



Modified from Gao et. al. Gastroenterology. 2011 Nov;141(5):1472-1585

Alcoholic Cirrhosis

- Prognosis
  - Depends on absence of decompensation, complications of portal hypertension, and abstinence
    - Compensated and abstinent: 5 year survival > 80%
    - Decompensation: 5 year survival >50%
    - Continued drinking: 5 year survival <50%
- Only established effective treatment is liver transplantation
- A major focus of evaluation is identifying those with low risk of recidivism

A·l·c·o·h·o·l

"The cause of - and solution to - all of life's problems."

NAFLD/NASH Outline

- The Metabolic Syndrome
- Terminology
- Risk Factors
- Epidemiology
- Mechanisms of Steatosis Formation and Disease Progression
- Clinical Workup
- Histopathology
- Treatment

The Metabolic Syndrome

- Waist circumference (35 inches female; 40 inches male)
  - BMI>30kg/m^2
- Diabetes
- Dislipidemia
- Hypertension
- **NAFLD: Non Alcoholic Fatty Liver Disease**
  - The hepatic manifestation of the metabolic syndrome
  - 90% of patients with NAFLD have one feature of the metabolic syndrome
  - 33% have three or more features

Non Alcoholic Fatty Liver Disease (NAFLD)

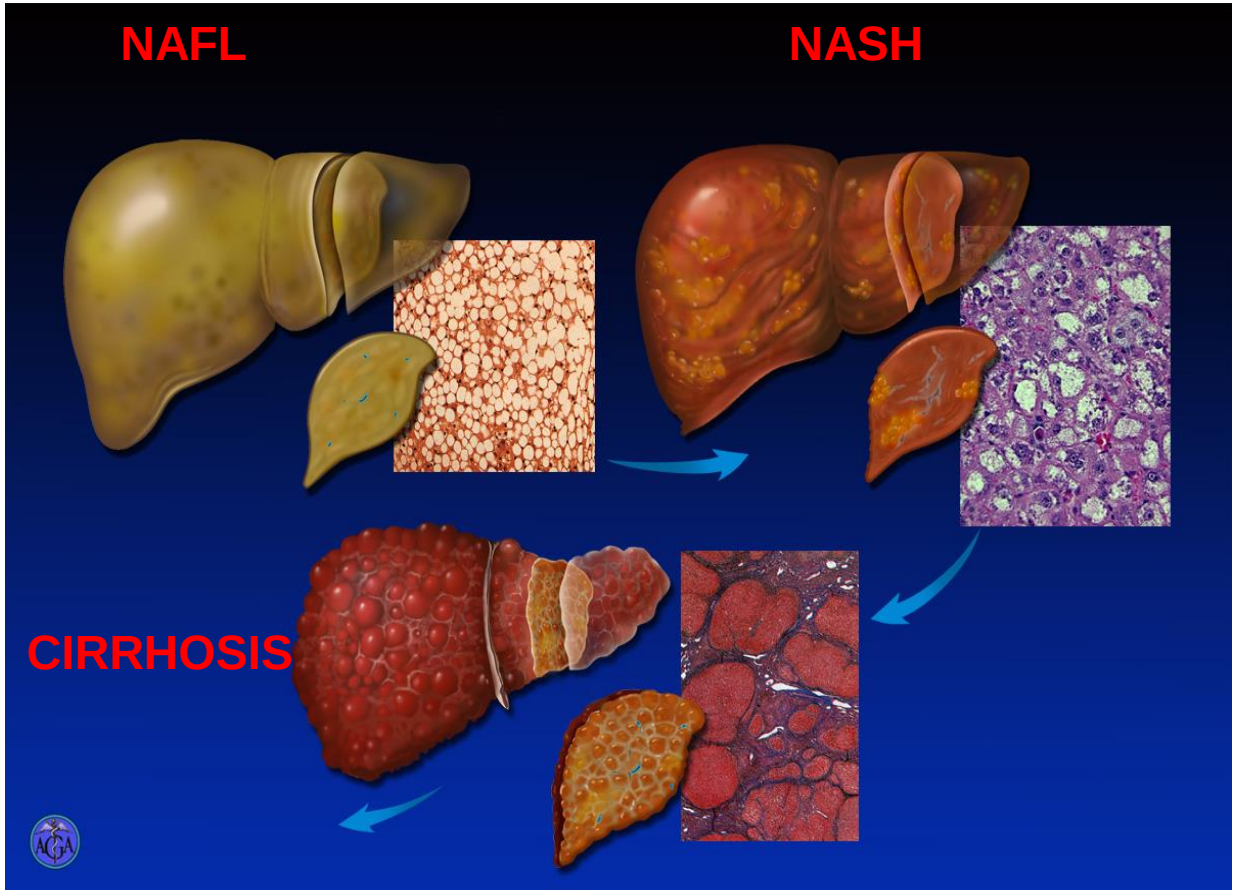
- Alcohol-like liver disease in individuals who DO NOT consume alcohol

NAFLD is the umbrella term which simply means steatosis (fat)

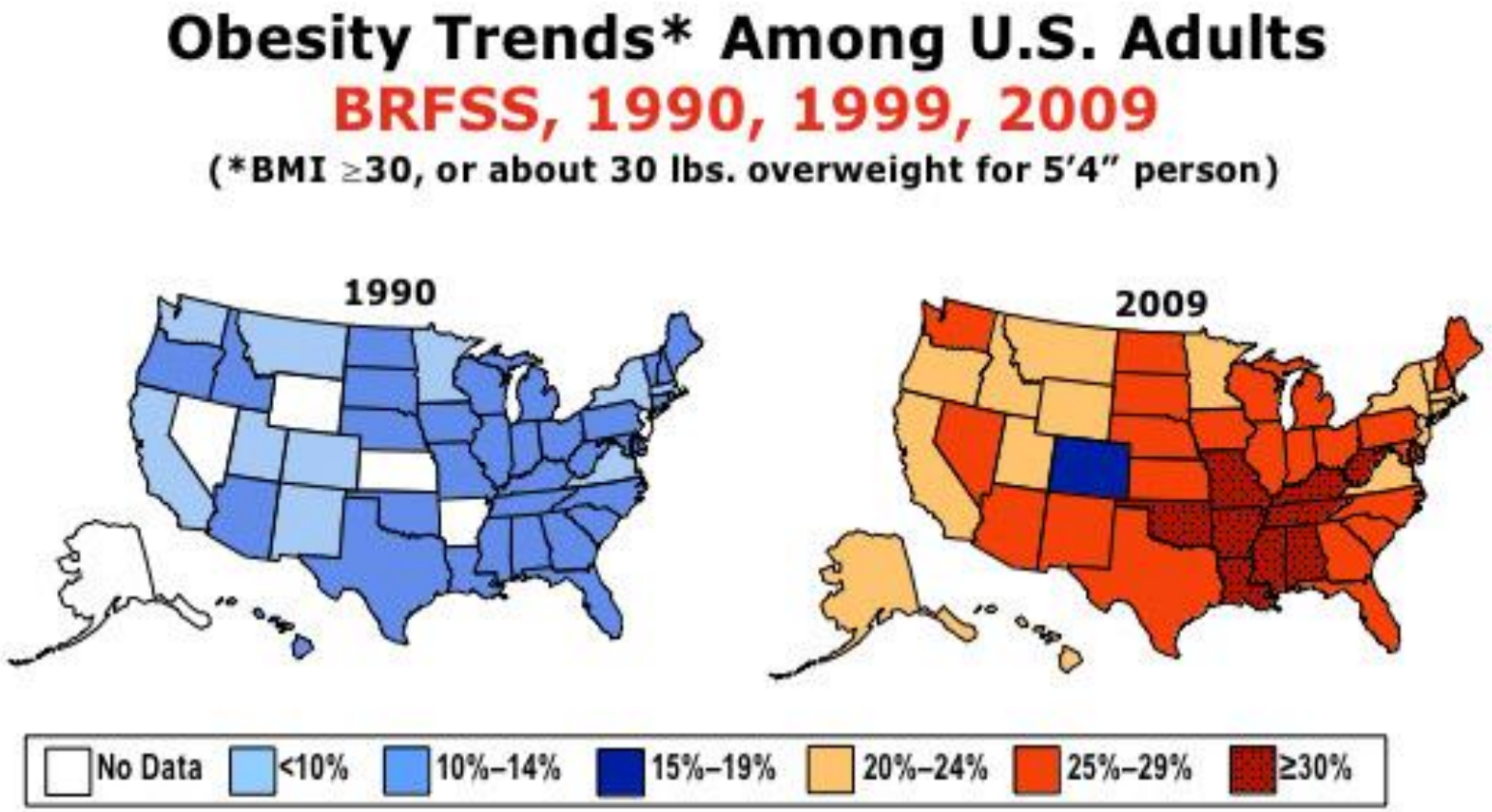
Subsets:
NAFL (simple steatosis)

NASH (steatosis and inflammation/cell death)

Cirrhosis (hepatic fibrosis)



Obesity as a Risk Factor



Source: Behavioral Risk Factor Surveillance System, CDC.

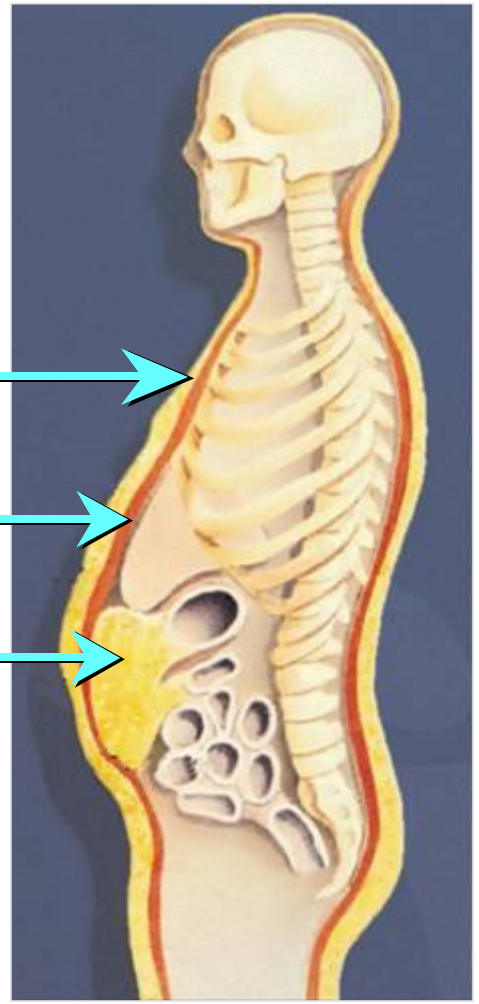
Central Adiposity is Key

~ 35% of the adult US population is obese

Obesity rates are highest among middle aged people; however, prevalence increasing in childhood

No significant differences in gender

Ethnicity plays a role: African American and Hispanic>>>Asians



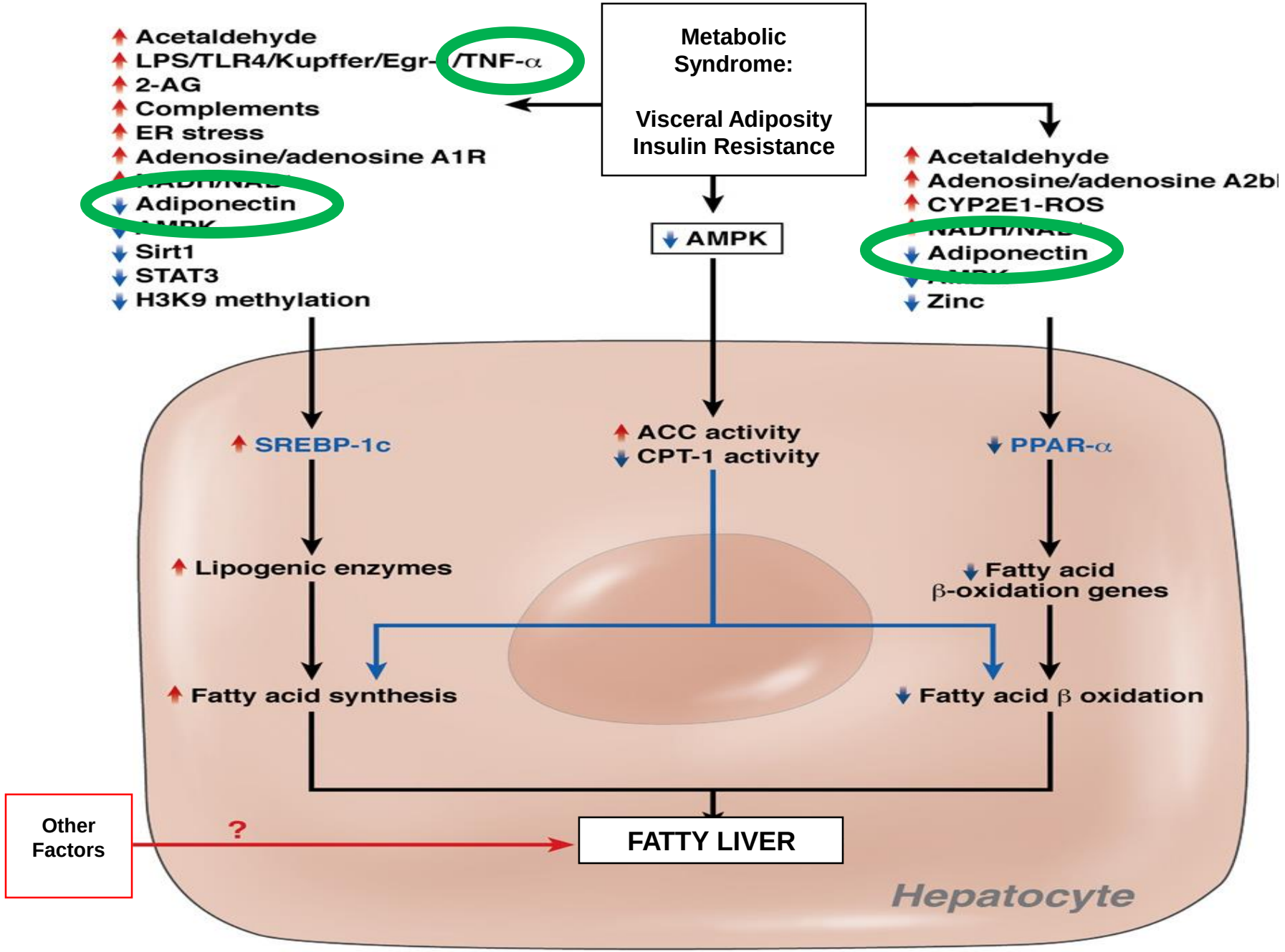
NAFLD Prevalence

- Dallas Heart Study
  - Assessed prevalence of NAFLD in 2,200 patients with *non-invasive imaging:* 31%
- NHANES III
  - Assessed prevalence of NAFLD in 15,700 patients with *aminotransferases:* 5%
- Why the discrepancy between Dallas and NHANES?
  - Many individuals (80%) with NAFLD do not exhibit abnormal aminotransferases
- The “Real” (or at least realer) truth:
  - 30% of the US adult population with NAFLD
  - 3-5% with NASH
  - NAFLD/NASH: most common liver disease in Western nations
  - Leading indication for liver transplantation by 2020

Putting Fat in the Liver: NAFLD Genesis

- Disorders that occur in the metabolic syndrome result from the abnormal production of hormones and cytokines that regulate inflammatory responses

- Individuals with the metabolic syndrome generally exhibit an excess of pro-inflammatory factors relative to anti-inflammatory factors


Metabolic Syndrome:
Visceral Adiposity
Insulin Resistance
Acetaldehyde
LPS/TLR4/Kupffer/Egr-/TNF-α
2-AG
Complements
ER stress
Adenosine/adenosine A1R
Adiponectin
Sirt1
STAT3
H3K9 methylation
AMPK
Acetaldehyde
Adenosine/adenosine A2b
CYP2E1-ROS
Adiponectin
Zinc
SREBP-1c
ACC activity
CPT-1 activity
PPAR-α
Lipogenic enzymes
Fatty acid β-oxidation genes
Fatty acid synthesis
Fatty acid β oxidation
Other Factors
?
FATTY LIVER
Hepatocyte

Cytokine Imbalance Promotes Steatosis and NASH

↑ TNF

Pro-inflammatory

- Pro-apoptotic
- Recruits WBC's
- Promotes insulin resistance

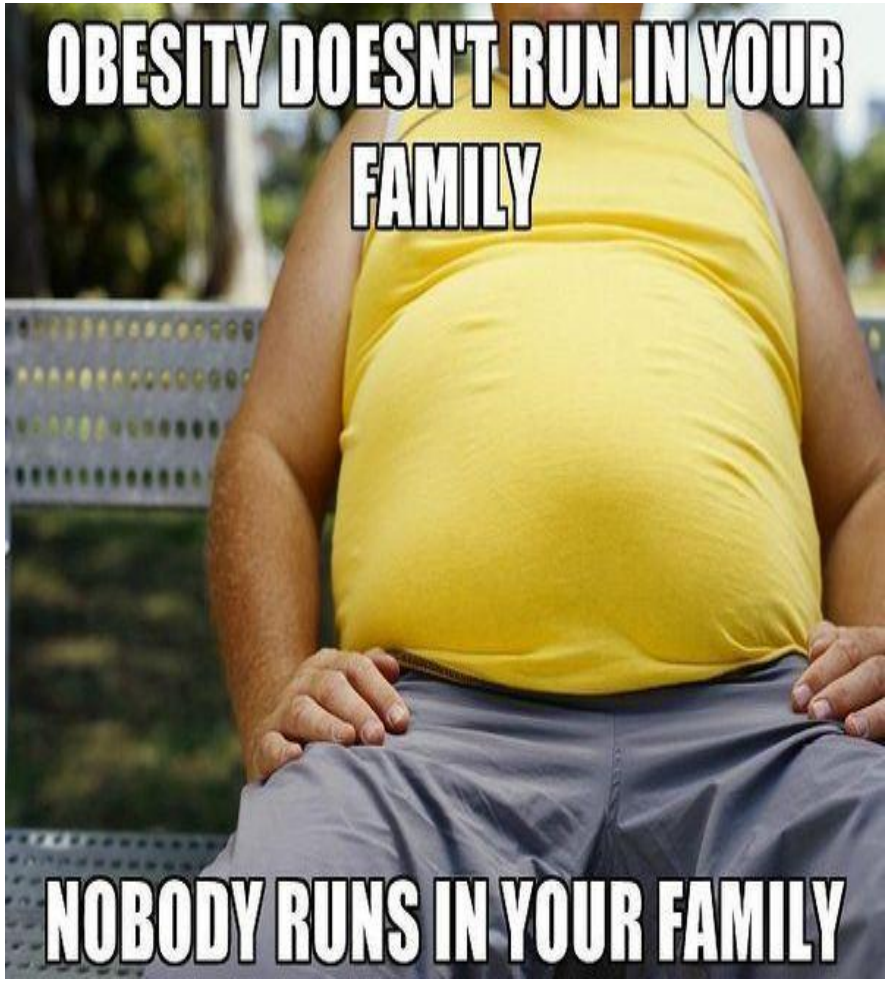
↓ Adiponectin

Anti-inflammatory

- Inhibits FA uptake
- Stimulates FA oxidation & lipid export
- Enhances insulin sensitivity

•Steatosis (NAFL)
•Cell Death and Inflammation (NASH)
•Insulin Resistance

Other Factors Involved in Steatosis and NASH Progression



- Genetics
  - Genome wide association studies in cohorts with NAFLD identified a polymorphism (rs738409) in PNPLA3 gene and liver fat content
  - PNPLA3 isoform (114M) disrupts triglyceride hydrolysis

Other Factors Involved in Steatosis and NASH Progression

- Diet
  - Composition of diet in particular:

    the type of lipid (mainly omega-6 fatty acids)

    &

    carbohydrates (mainly fructose)

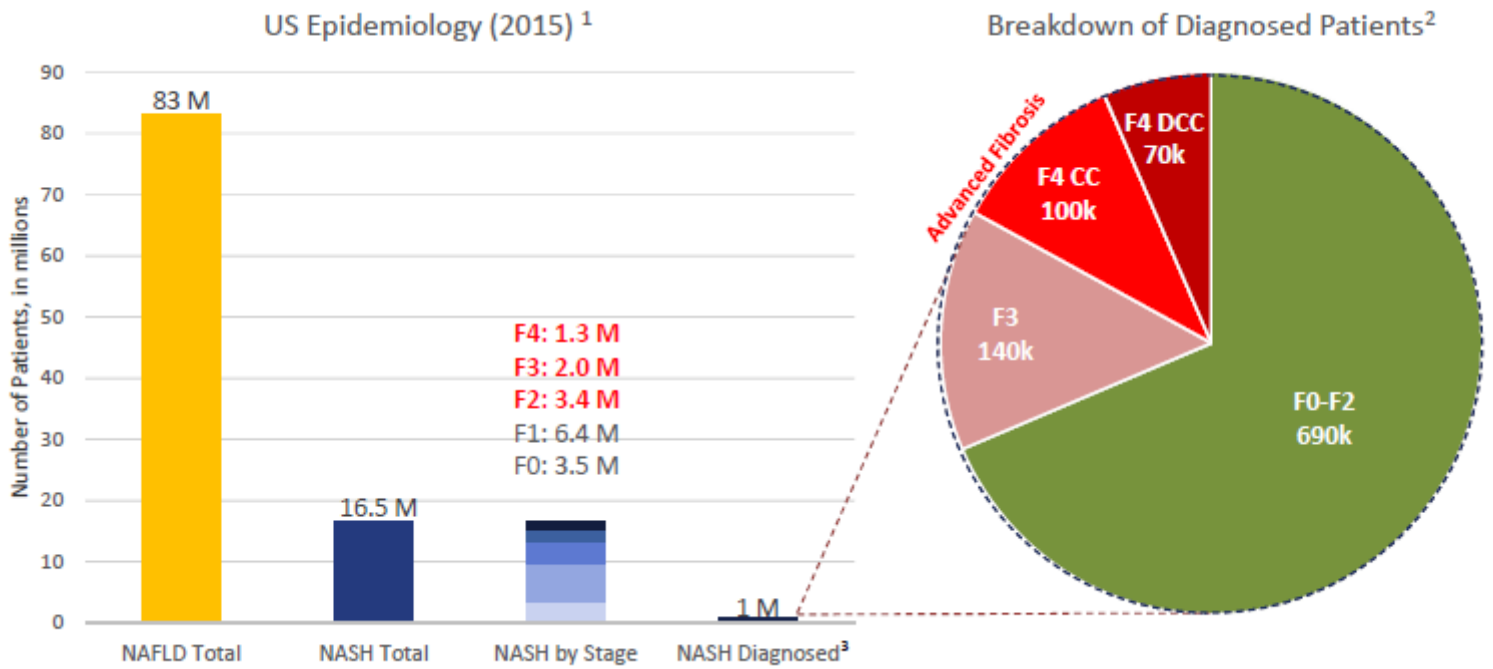
    play a role in progression to NASH

Other Factors (continued)

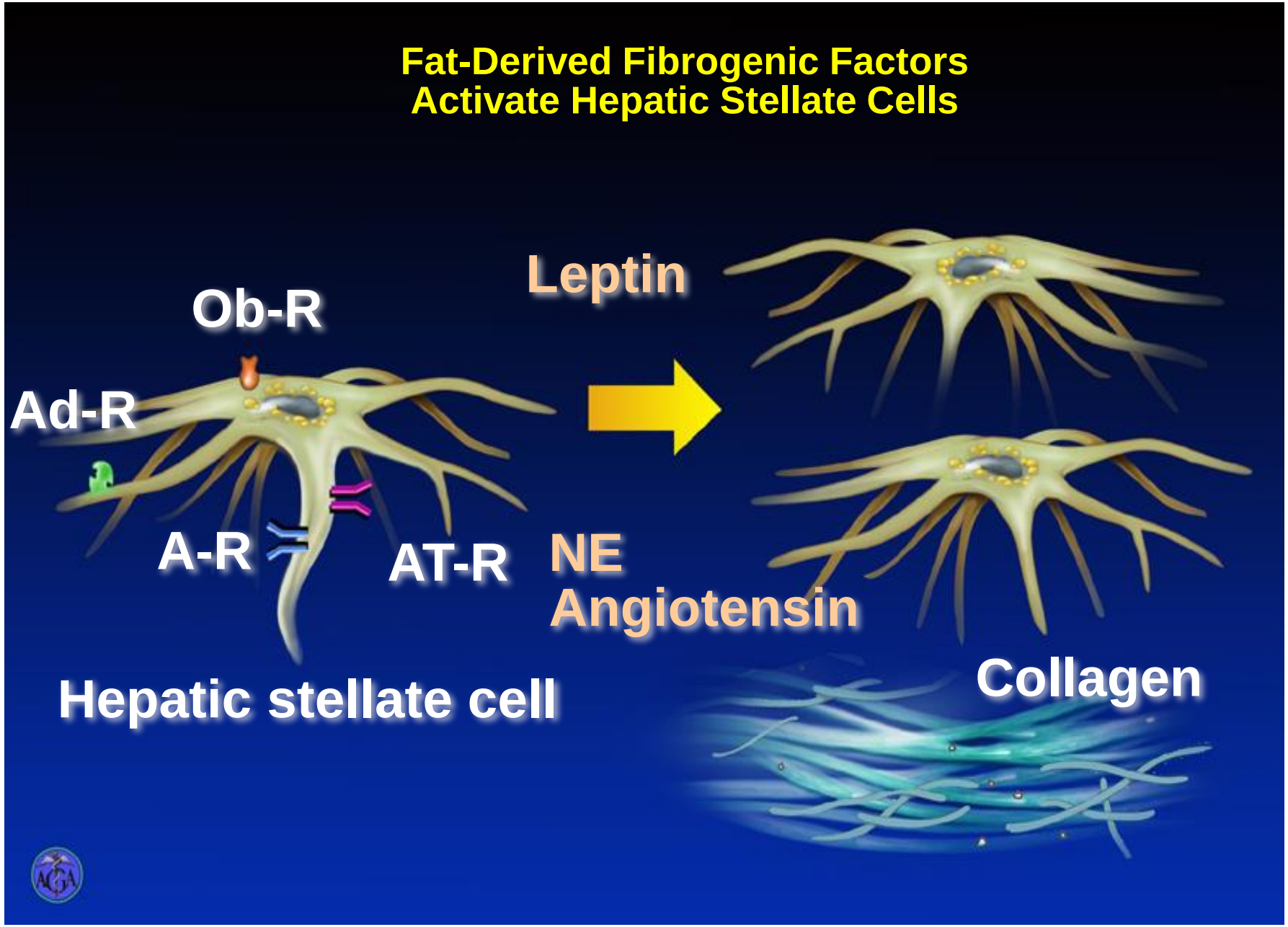
- Gut microflora
  - Involved in digestion
  - Modulates innate immunity and cytokine balance

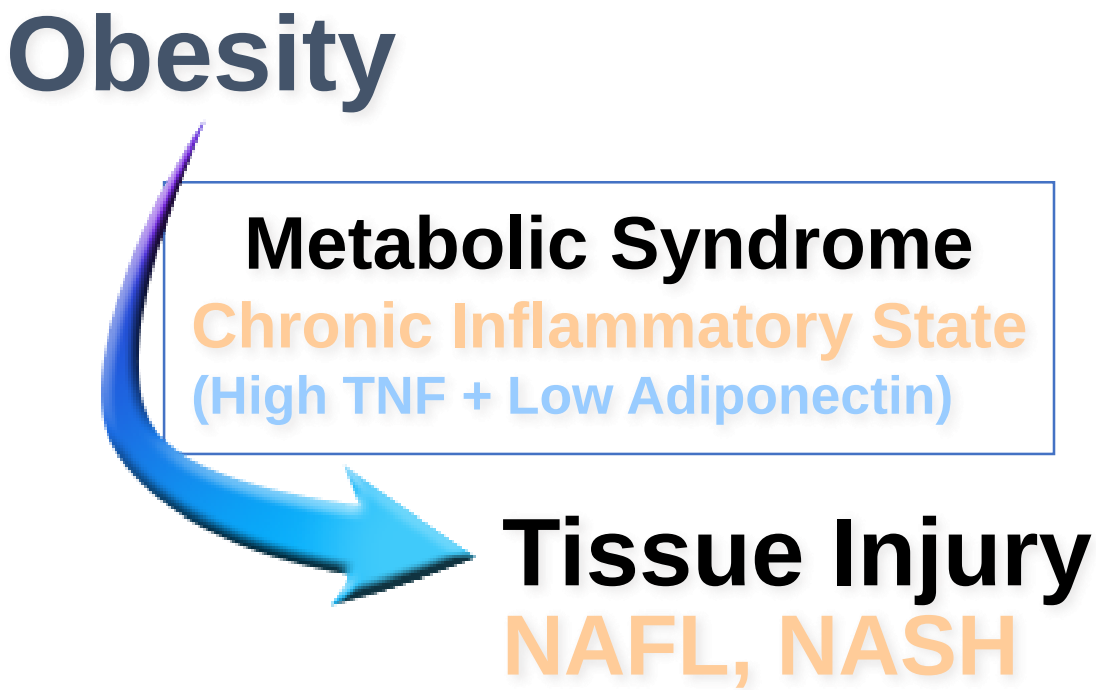
- Concomitant liver conditions
  - Alcohol use
  - Chronic virus: Hepatitis B and Hepatitis C

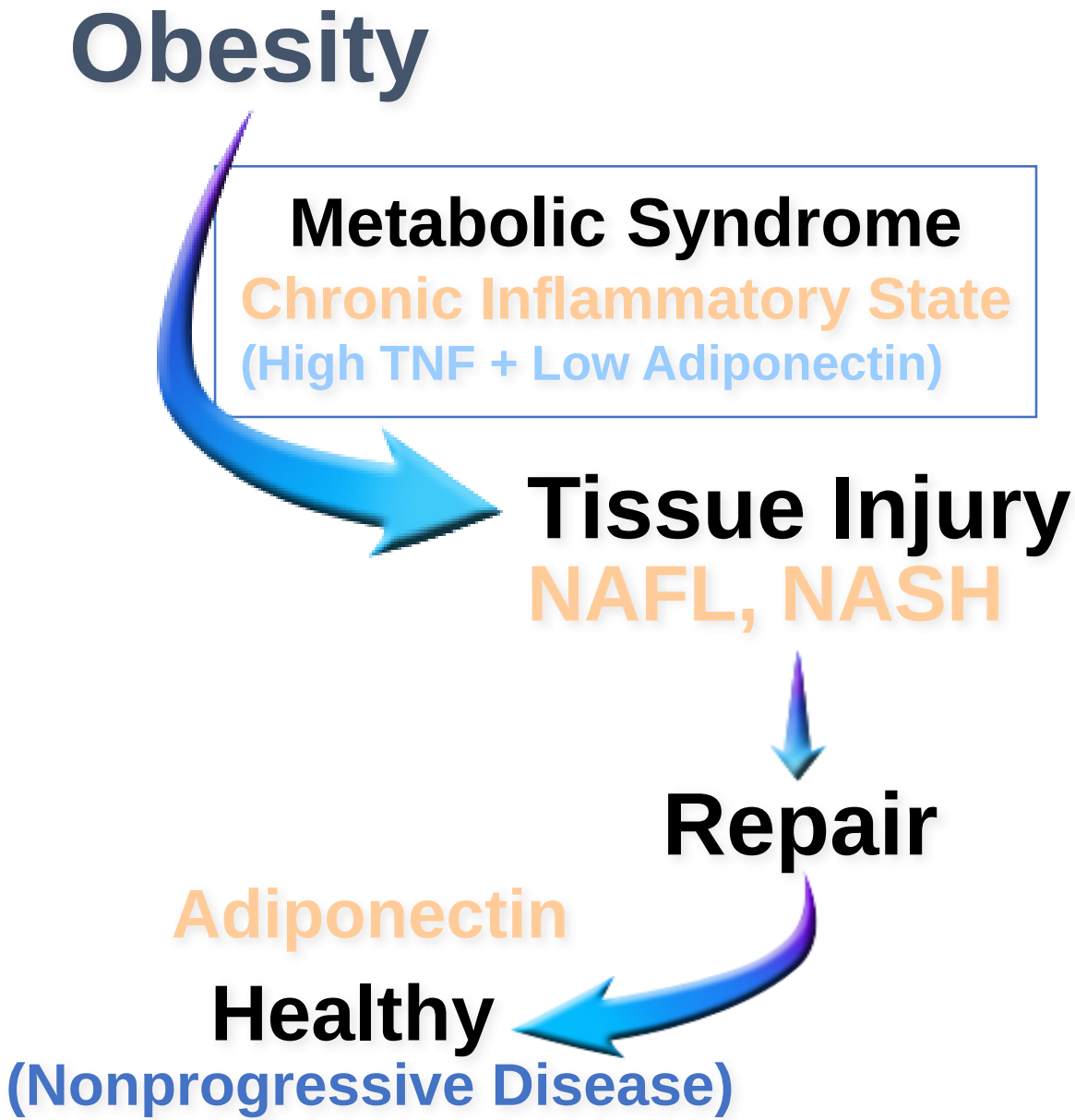
Prevalence of NASH with advanced fibrosis

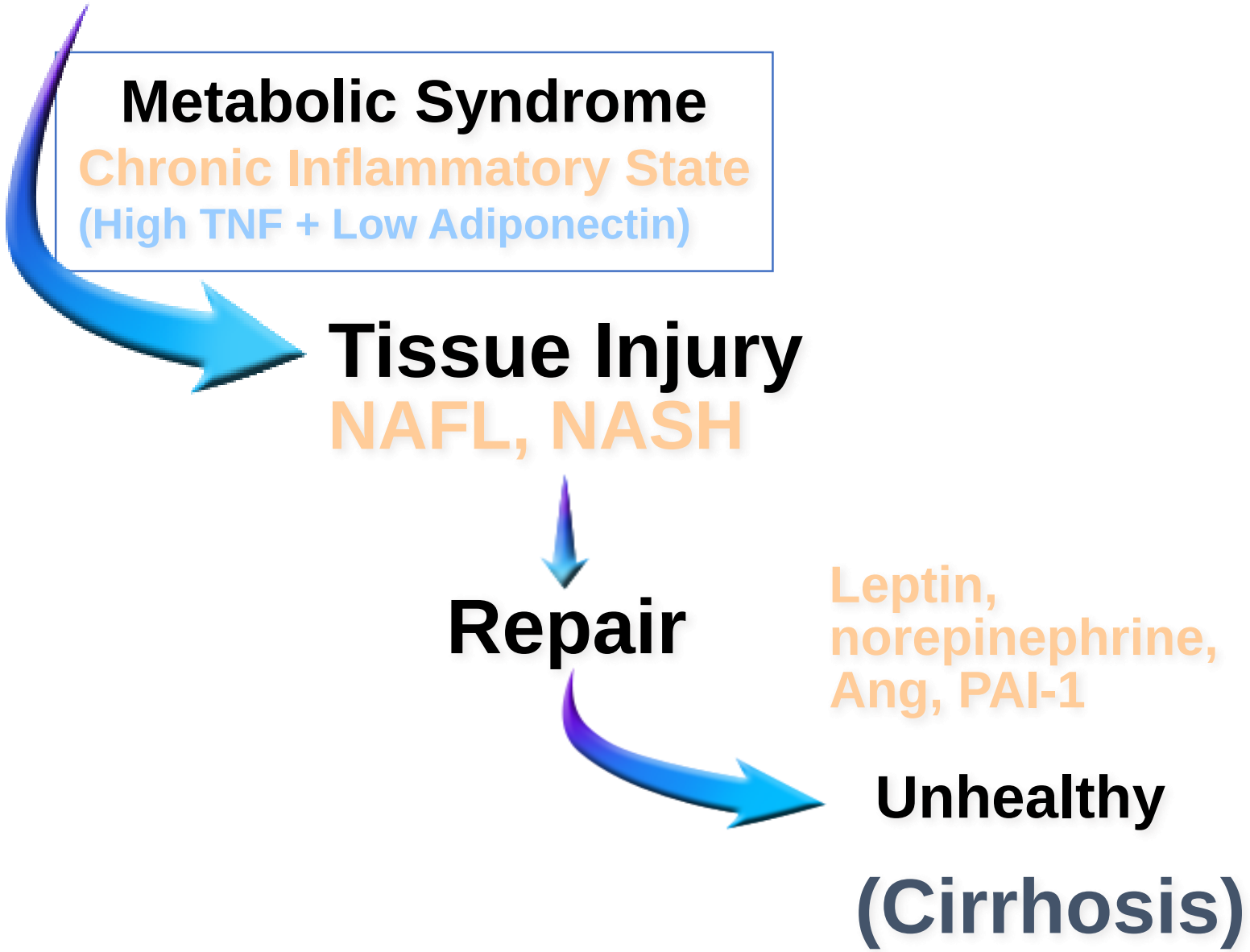


Source: 1. Estes, et al. Hepatology. 2017.
2. Average fibrosis distributions from 9 published studies (N=699). 3. Global NASH Epidemiology Study 2016 Total diagnosed NASH population (US claims and electronic medical records analyses (Humedica, Pharmetrics and SHA)


Fat-Derived Fibrogenic Factors
Activate Hepatic Stellate Cells
Ob-R
Ad-R
A-R
AT-R
Leptin
NE
Angiotensin
Collagen
Hepatic stellate cell


Obesity
Metabolic Syndrome
Chronic Inflammatory State
(High TNF + Low Adiponectin)
Tissue Injury
NAFL, NASH


Obesity
Metabolic Syndrome
Chronic Inflammatory State
(High TNF + Low Adiponectin)
Tissue Injury
NAFL, NASH
Repair
Adiponectin
Healthy
(Nonprogressive Disease)


Metabolic Syndrome
Chronic Inflammatory State
(High TNF + Low Adiponectin)
Tissue Injury
NAFL, NASH
Repair
Leptin,
norepinephrine,
Ang, PAI-1
Unhealthy
(Cirrhosis)

SUMMARY

- The metabolic syndrome and associated insulin resistance leads to signaling in the liver that promotes:
  - Generation and storage of fat
  - Pro-Inflammatory cytokines
  - Liver cell injury and death
  - Deposition of collagen and development of cirrhosis

- The progression of disease is dependent upon a number of cofactors including:
  - Genetics
  - Diet
  - Gut microbia
  - Concomitant liver conditions

NAFLD/NASH: Clinical and Laboratory Findings

- Symptoms
  - Usually Asymptomatic
  - Rarely causes RUQ

- Signs/Findings
  - Hepatomegaly
  - Elevated AST/ALT up to 2-5 fold
  - ALT>AST in the majority of cases
  - Elevated ALK PHOS in up 30%
  - Elevated Ferritin 50-60%
  - Fatty liver noted on imaging (ultrasound/CT scan/MRI)

NAFLD/NASH Diagnostic Criteria/Workup

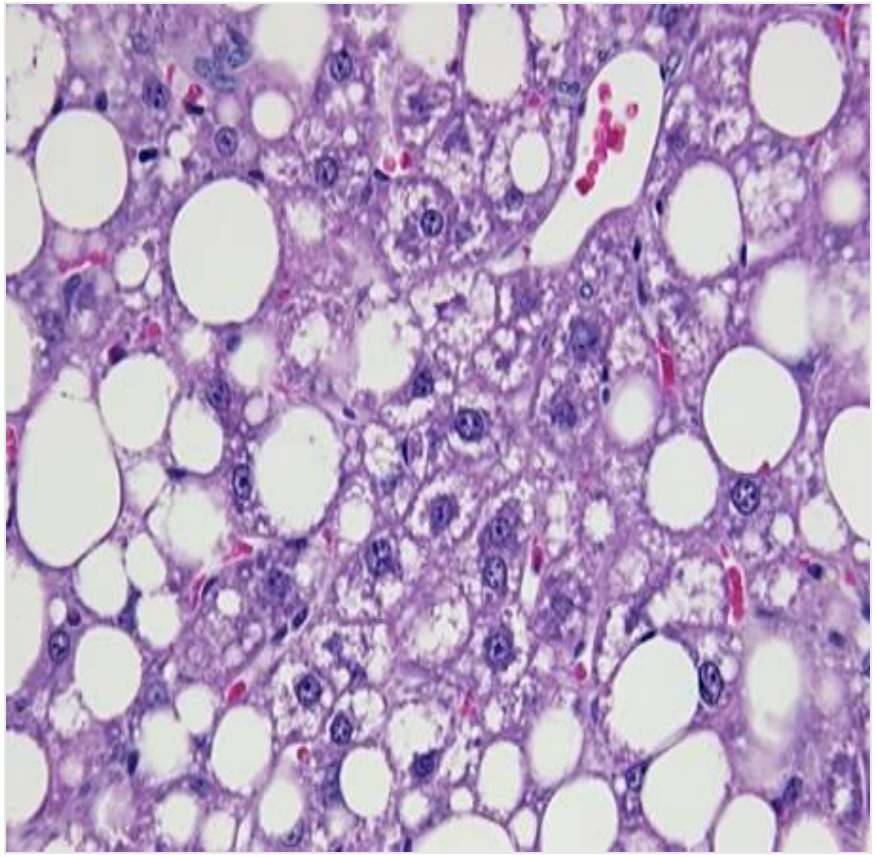
- A diagnosis of exclusion

- History and Lab evaluation
  - No excessive alcohol intake (<10 to 20g/day)
  - Chronic virus assessment (Hep B and Hep C)
  - Negative autoimmune markers (ANA, Anti-Smooth, Anti-Mitochondrial)
  - Normal TSH
  - Normal ceruloplasmin

Abdominal Imaging

- Ultrasound
  - Simple, readily available
  - Operator dependent
  - Looking for increased echogenicity (brightness)
  - Sensitivity increases with increasing amounts of fat
- Cross-sectional Imaging
  - CT scan or MRI
- Non-Invasive Methods for Fibrosis
  - MR Elastography: evaluates degree of fibrosis/cirrhotic change
  - MR Spectroscopy: measures amount of macrovesicular fat

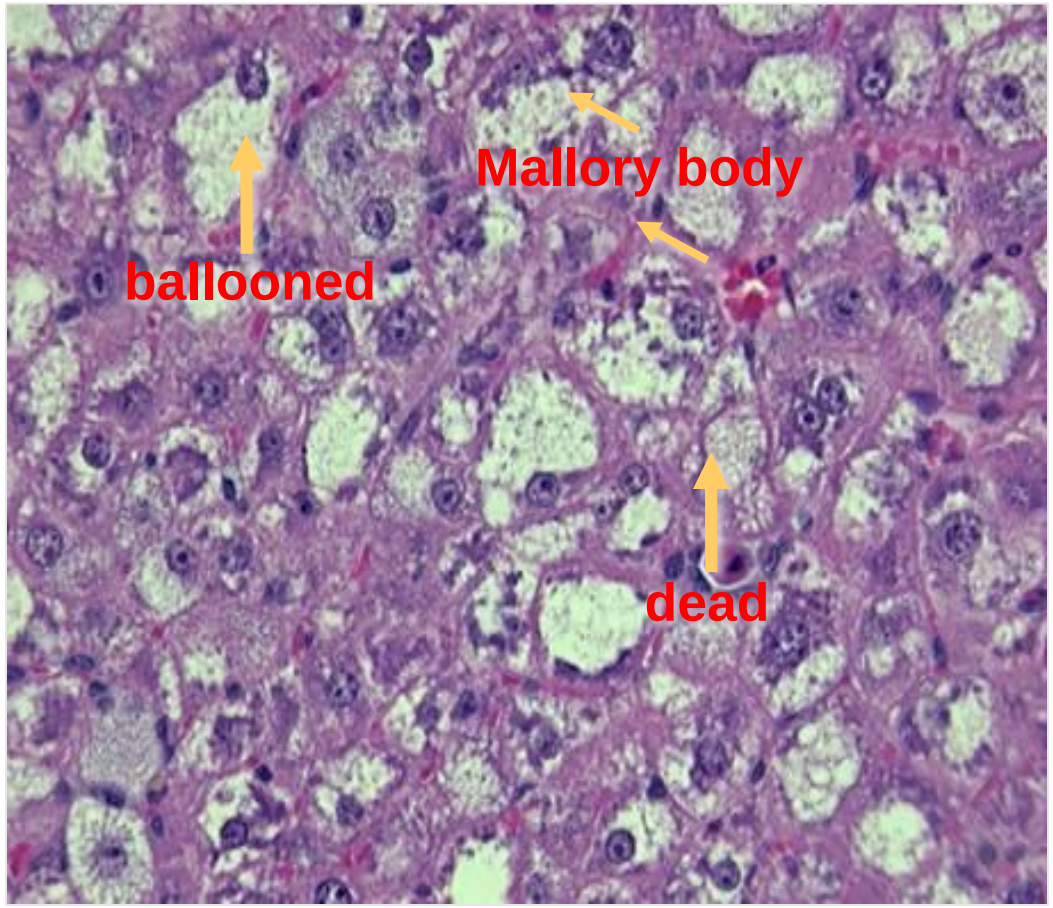
Fatty Liver Disease Histopathology
Simple Steatosis (NAFL)



- **Inconspicuous**
  - Cell death
  - Inflammation
- **Increased ROS**
- **Induced**
  - Anti-oxidant &
  - Survival responses

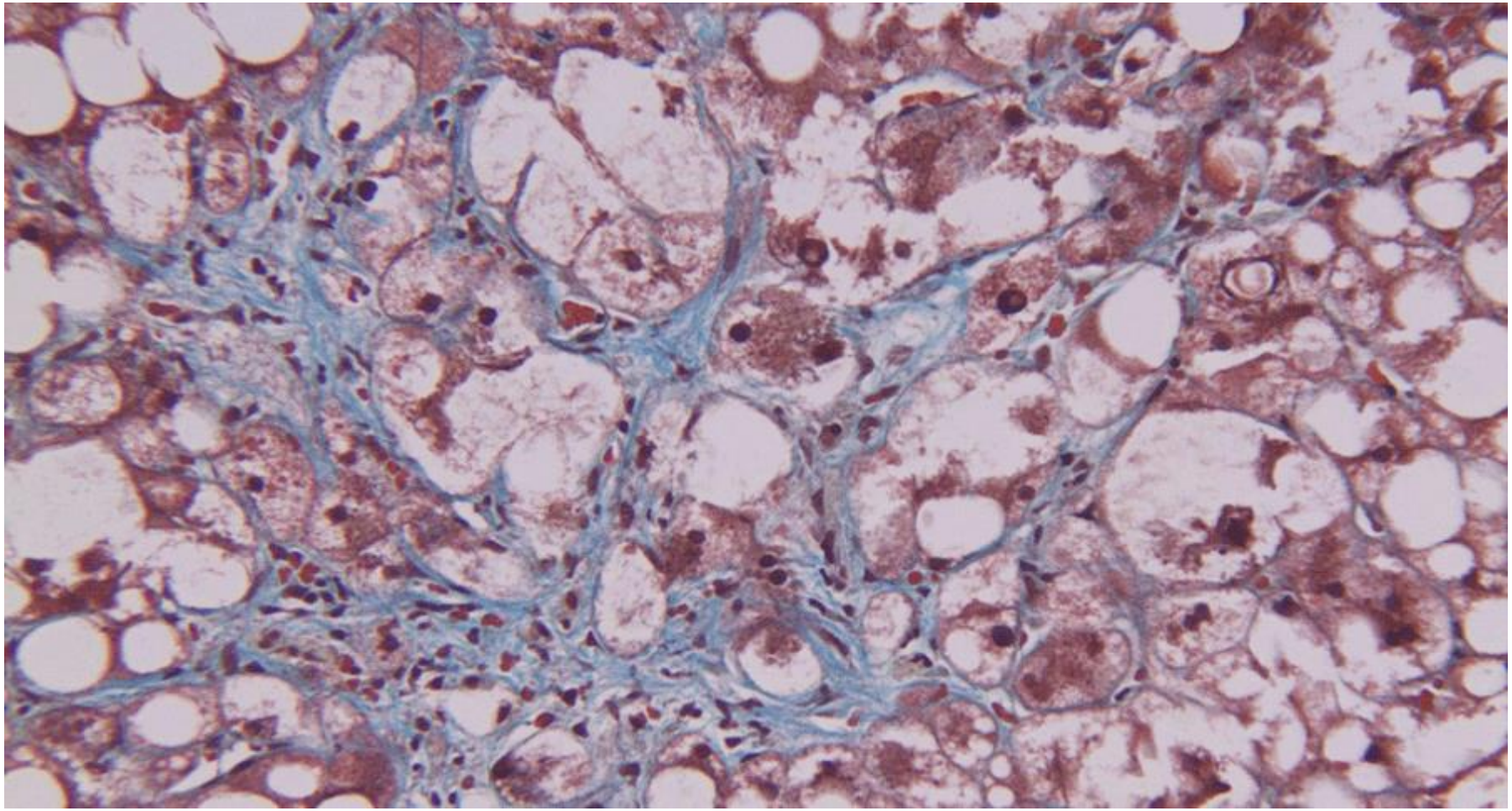
Fatty Liver Disease Histopathology: Steatosis/inflammation (NASH)

Steatohepatitis

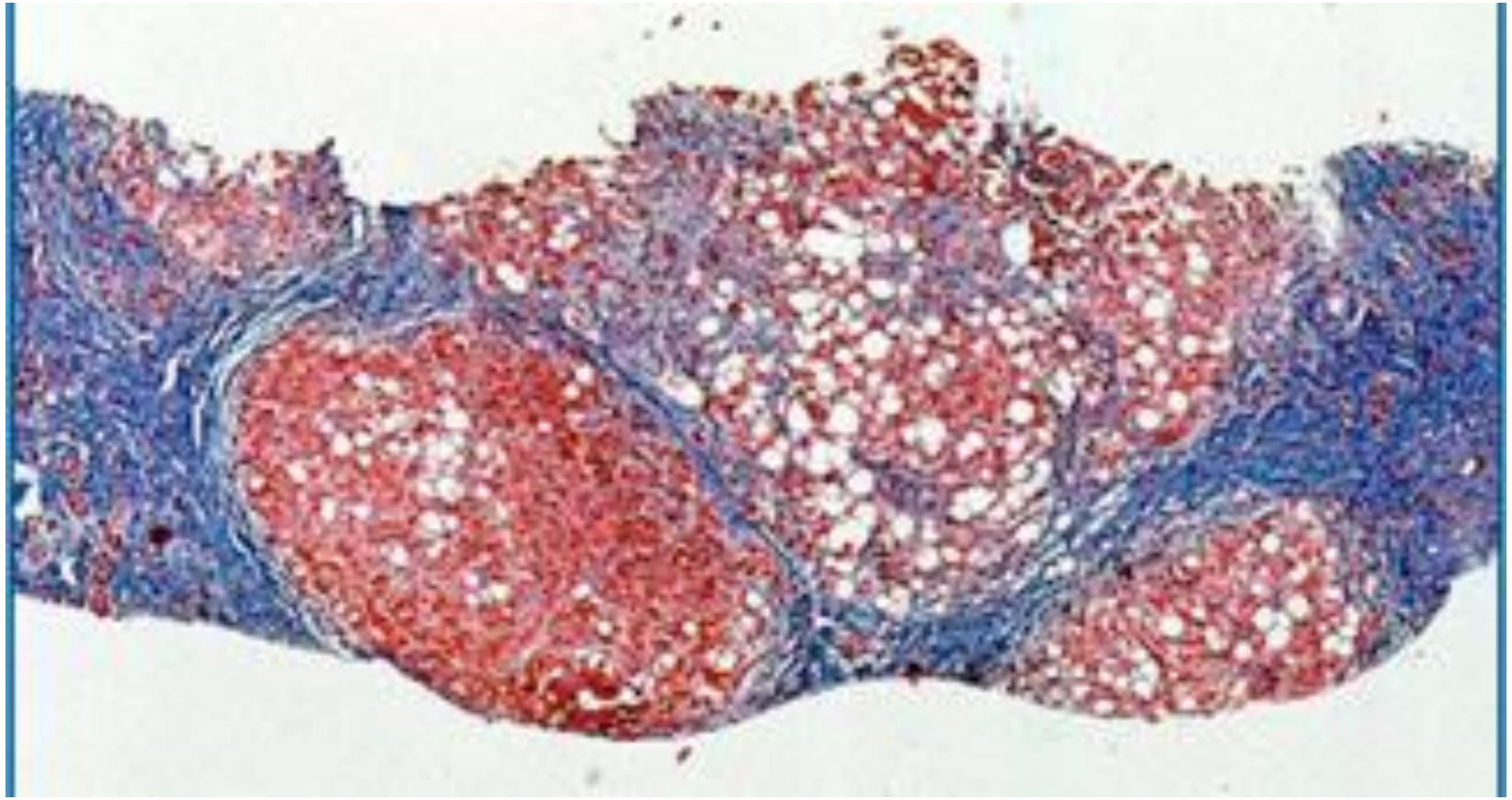


- **Hepatocyte injury**
  - Ballooning
  - Mallory bodies
  - Dead cells
- **Inflammatory cell**
  - Infiltration
- **Overwhelmed**
  - Anti-oxidant &
  - Survival responses

NASH PATTERN OF FIBROSIS



NASH Cirrhosis Biopsy



Treatment of NAFLD/NASH

- General Principle:
  - Treat and prevent the development of metabolic syndrome

- Diet and Exercise—THE CORNERSTONE
- Diabetes
  - Metformin, TZDs
- Lipid lowering agents
  - Statins and fibrates
- Anti-hypertensives
  - ACE-inhibitors, angiotensin receptor blockers

- Surprisingly, the individual effect of any agent on steatosis or steatohepatitis isn’t well established

Treatment of NAFLD/NASH

- Diet
  - Patients have increased caloric intake, tend to have higher carbohydrate intake and fats
  - Avoidance of high fructose corn syrup
  - Mediterranean diet may be helpful

- Exercise
  - Aerobic physical exercise 30 minutes a day (5x/week)
  - Beneficial effect irrespective of weight loss

Treatment of NAFLD/NASH

- Clear link between DM and NASH

- Metformin
  - No significant effect on histology; not recommended

- Thiazolidinedione (TZDs)
  - Short term trials have yielded variable results
  - May improve inflammation, steatosis but NOT fibrosis
  - Long term safety and efficacy is unclear

Treatment of NAFLD/NASH

- Vitamin E
  - RCT, 84 patients randomized to 800 IU daily
  - Decreased in aminotransferases
  - Improvement in steatosis but NOT fibrosis
  - Has gained acceptance in clinical practice in non-diabetic patients with NASH
  - Similarly positive trend when combined with pioglitazone but larger incidence of weight gain

Treatment of NAFLD/NASH

- HMG-CoA Reductase Inhibitors
  - Great for lipids, not for NASH
- Ursodeoxycholic Acid
  - Doesn’t work
- Orlistat
  - Linked to hepatic injury/poorly tolerated

NAFLD/NASH Pharmacotherapy

- Farnesoid X Receptor (FXR) Agonists
  - Nuclear hormone receptors involved in the metabolism of bilirubin
  - Regulate gene expression for cholesterol 7 alpha-hydroxylase (rate limiting enzyme in bile acid synthesis)
  - Bile acids are endogenous ligands and FXR plays a critical role metabolism
  - Obeticholic acid high potency bile acid shown to be protective in NAFLD/NASH

Treatment of NAFLD/NASH

- Bariatric Surgery
  - Roux en Y gastric bypass common
  - Resolution of steatosis and steatohepatitis in many studies
  - Durability of results in question
  - Those with advanced fibrosis may have complications after surgery

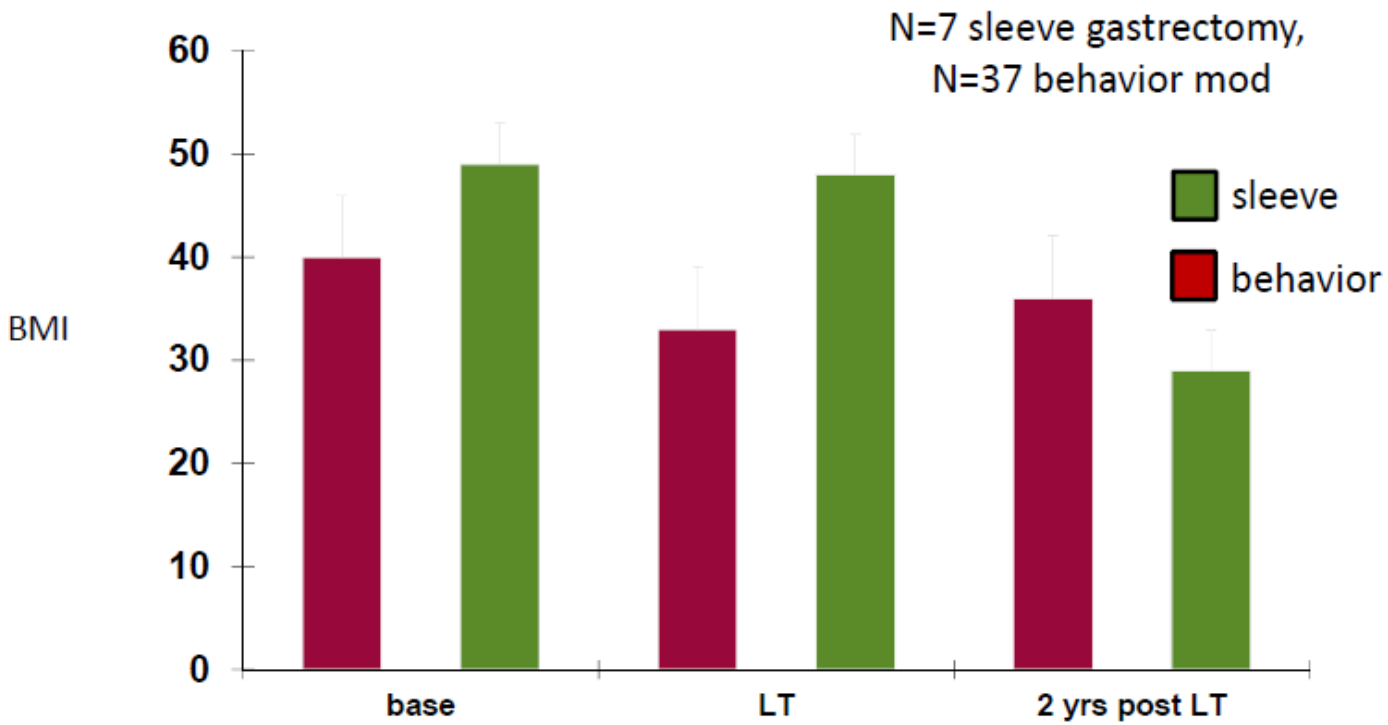
Frequency and Type of Bariatric Surgery in United States

Published June 2018

	2011	2012	2013	2014	2015	2016	2017
Total	**158,000**	**173,000**	**179,000**	**193,000**	**196,000**	**216,000**	**228,000**
Sleeve	17.80%	33.00%	42.10%	51.70%	53.61%	58.11%	**59.39%**
RYGB	36.70%	37.50%	34.20%	26.80%	23.02%	18.69%	**17.80%**
Band	35.40%	20.20%	14.00%	9.50%	5.68%	3.39%	**2.77%**
BPD-DS	0.90%	1.00%	1.00%	0.40%	0.60%	0.57%	**0.70%**
Revision	6.00%	6.00%	6.00%	11.50%	13.55%	13.95%	**14.14%**
Other	3.20%	2.30%	2.70%	0.10%	3.19%	2.63%	**2.46%**
Balloons	–	–	–	–	0.36%	2.66%	**2.75%**

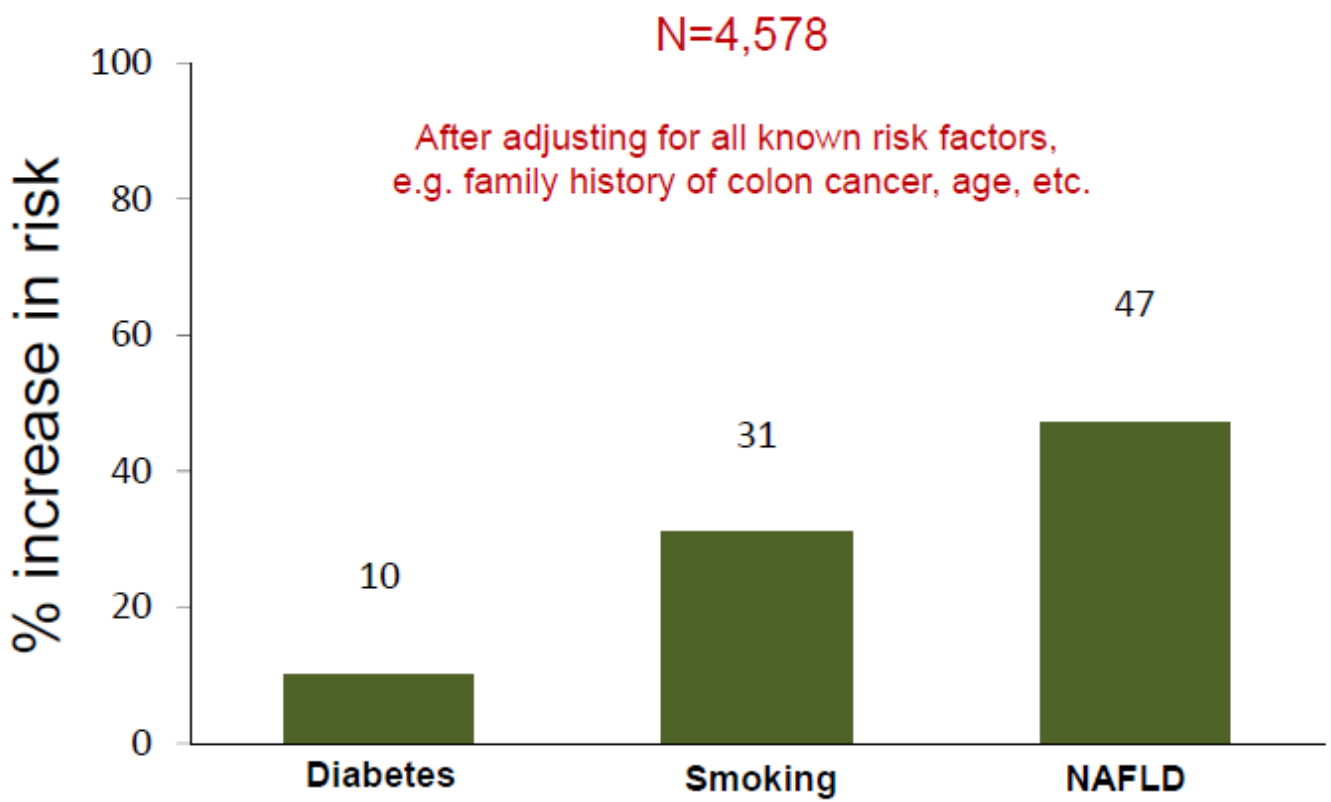
The ASMBS total bariatric procedure numbers are based on the best estimation from available data (BOLD,ACS/MBSAQIP, National Inpatient Sample Data and outpatient estimations).

Impact of Simultaneous Sleeve Gastrectomy



Heimbach et al., *AJT* 2012.

NAFLD as a Risk Factor for Colon Cancer on Follow-Up Colonoscopy



Yang et al., *PLoS One*. 2017; 12(8).

Summary

- NAFLD is the “hepatic manifestation” of the metabolic syndrome and obesity is the biggest risk factor
- The evolution from NAFLD to NASH to cirrhosis is complex and there are many co-factors
- NAFLD is a diagnosis of exclusion: imaging can provide clues and biopsy demonstrates macrovesicular steatosis without or with (NASH) inflammation
- Diet and exercise are cornerstones of treatment

References

- Chalasani et. al. AASLD Guidelines: Diagnosis and Management of NAFLD. Hepatology, Vol. 55, No. 6, 2012; pp: 2005-13

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- Paredes AH, Torres DM, **Harrison** SA. Nonalcoholic fatty liver disease. Clin Liver Dis. 2012 May;16(2):397-419.

- Illustrations from GastroSlides: NAFLD, accessed AGA.org 7/2014