Non-Alcoholic Fatty Liver Disease

Pathophysiology, Diagnosis, and Treatment

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Learning objectives:

1. Epidemiology of Non-Alcoholic Fatty Liver Disease (NAFLD)
2. Pathophysiology of NAFLD
3. Diagnosis of NALFD
4. Treatment and Management of NAFLD

Non-Alcoholic Fatty Liver Disease:
Definition

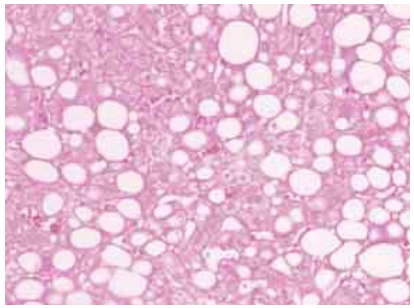
- Hepatic steatosis in the absence of secondary causes of hepatic fat accumulation:
  - significant alcohol consumption:
    - >21 drinks per week in men
    - >14 drinks per week in women
  - long-term use of medications known to cause steatosis
  - other chronic liver diseases

NAFLD:

Epidemiology

- Most prevalent cause of liver disease in the developed world:
  - Affects 25% of the world's population:
    - South America and Middle East: 31-32%
    - Northern Africa: 14%
  - Affects 30% of the U.S. population
- Second most common cause of end stage liver disease and need for liver transplantation in the U.S.
  - Predicted to become the most common indication for liver transplantation in the next decade
- Third most common cause of hepatocellular carcinoma in the U.S.

Kalia H. Clin Liver Dis. 2016



Non-Alcoholic Fatty Liver Disease

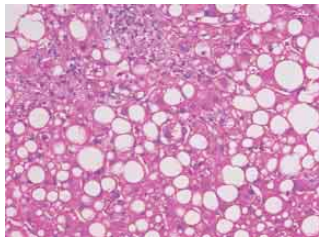
80%

Non-Alcoholic Fatty Liver (NAFL)

(Simple Steatosis)

20%

Non-Alcoholic Steatohepatitis (NASH)

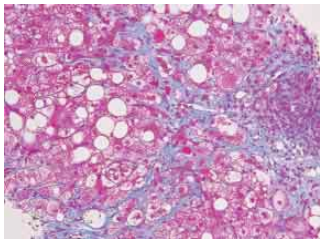


Fibrosis Stage: 0

Risks for progression:

- Age
- Increased BMI
- DMII

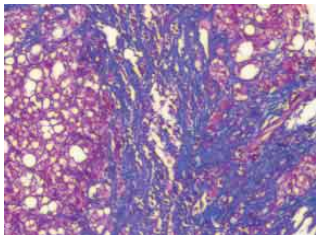
NASH with fibrosis



Fibrosis Stage: 2-3

20%

NASH cirrhosis



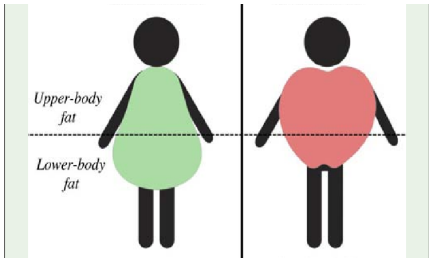
Fibrosis Stage: 4

Images: Rinella ME. JAMA. 2015

NAFLD:

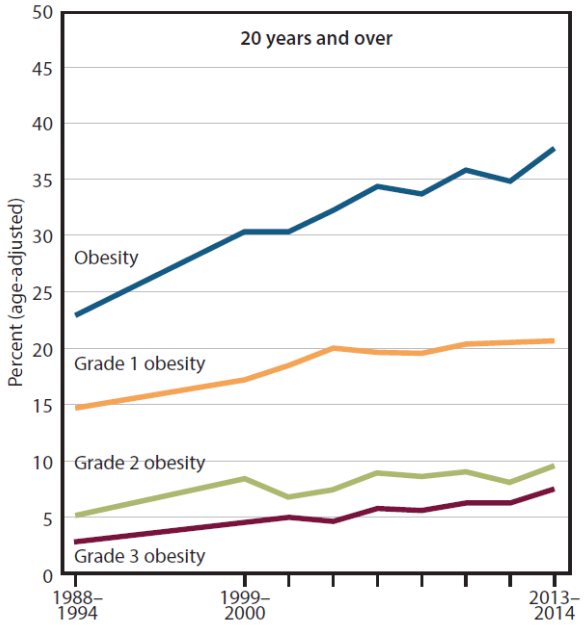
Risk Factors

- Obesity: BMI >30
- DMII/Metabolic Syndrome



- Age >45
- Hispanic Ethnicity

Prevalence of Obesity



SOURCE: NCHS, *Health, United States, 2016*,
Data from the NHANES.

Kalia H. Clin Liver Dis. 2016

NAFLD:

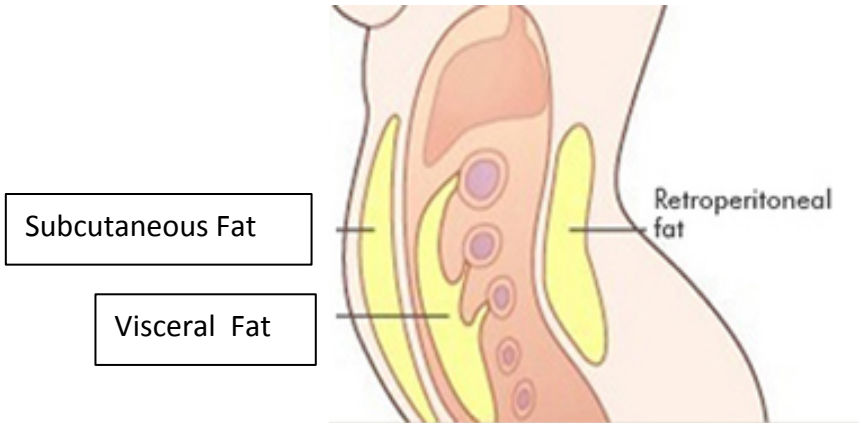
Prevalence in High Risk Populations

Population	NAFLD Prevalence
Morbid Obesity	~90% in bariatric surgery patients
DMII	60-70%
Metabolic Syndrome	53%
Dyslipidemia	50%
Male Gender	2x female
Hispanic Ethnicity	45-50%

Lonardo A. Digestive and Liver Dis. 2015

Non-obese NAFLD:

- Prevalence of NAFLD:
  - Lean NAFLD: 20% people with BMI <25
  - Non-obese NAFLD: 27% people with BMI <30
- Risk factors:
  - Visceral Obesity → Insulin resistance



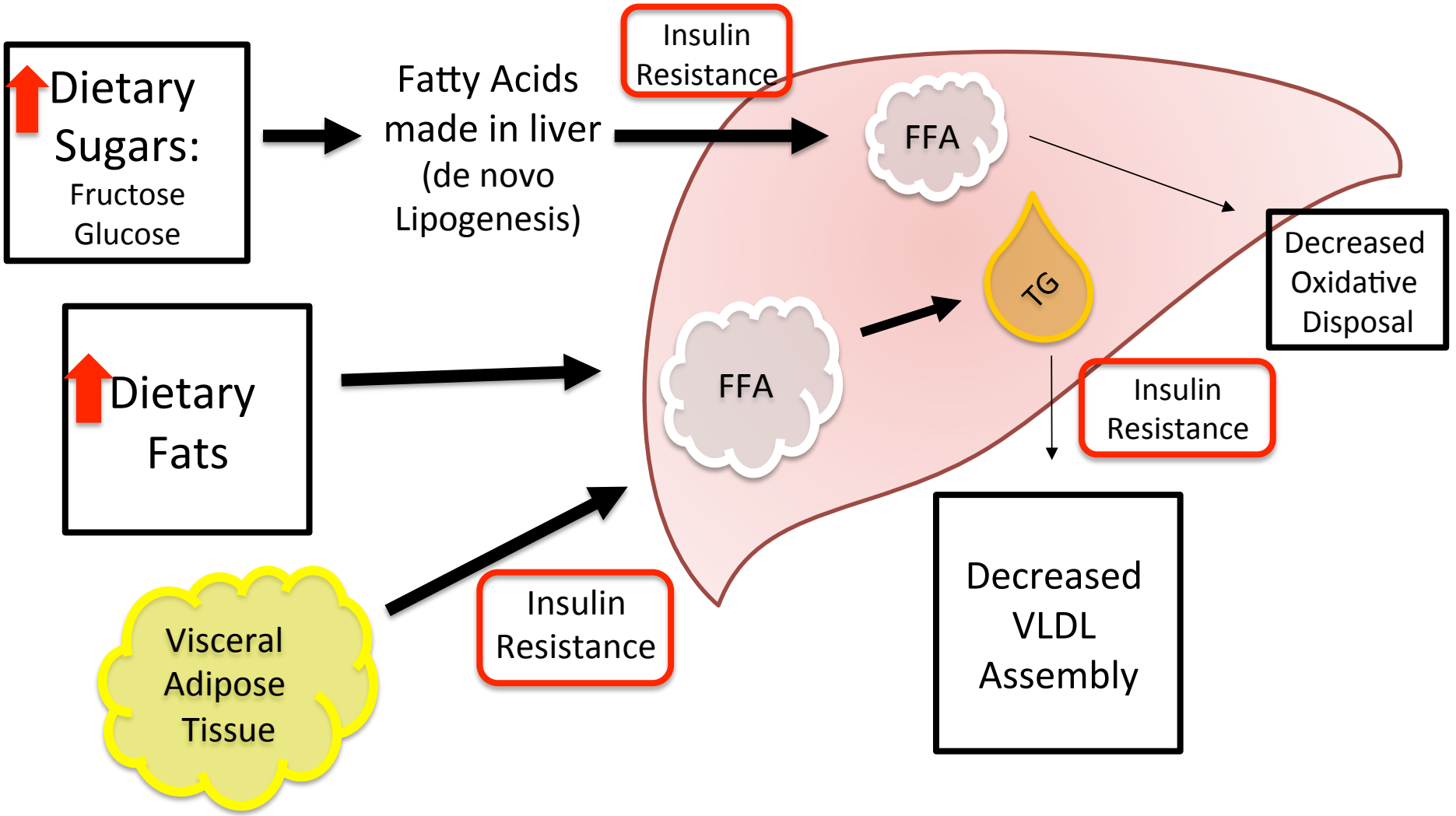
Kim D. Hepatology 2012

Unhealthy Diet and Inactivity in NAFLD/NASH:

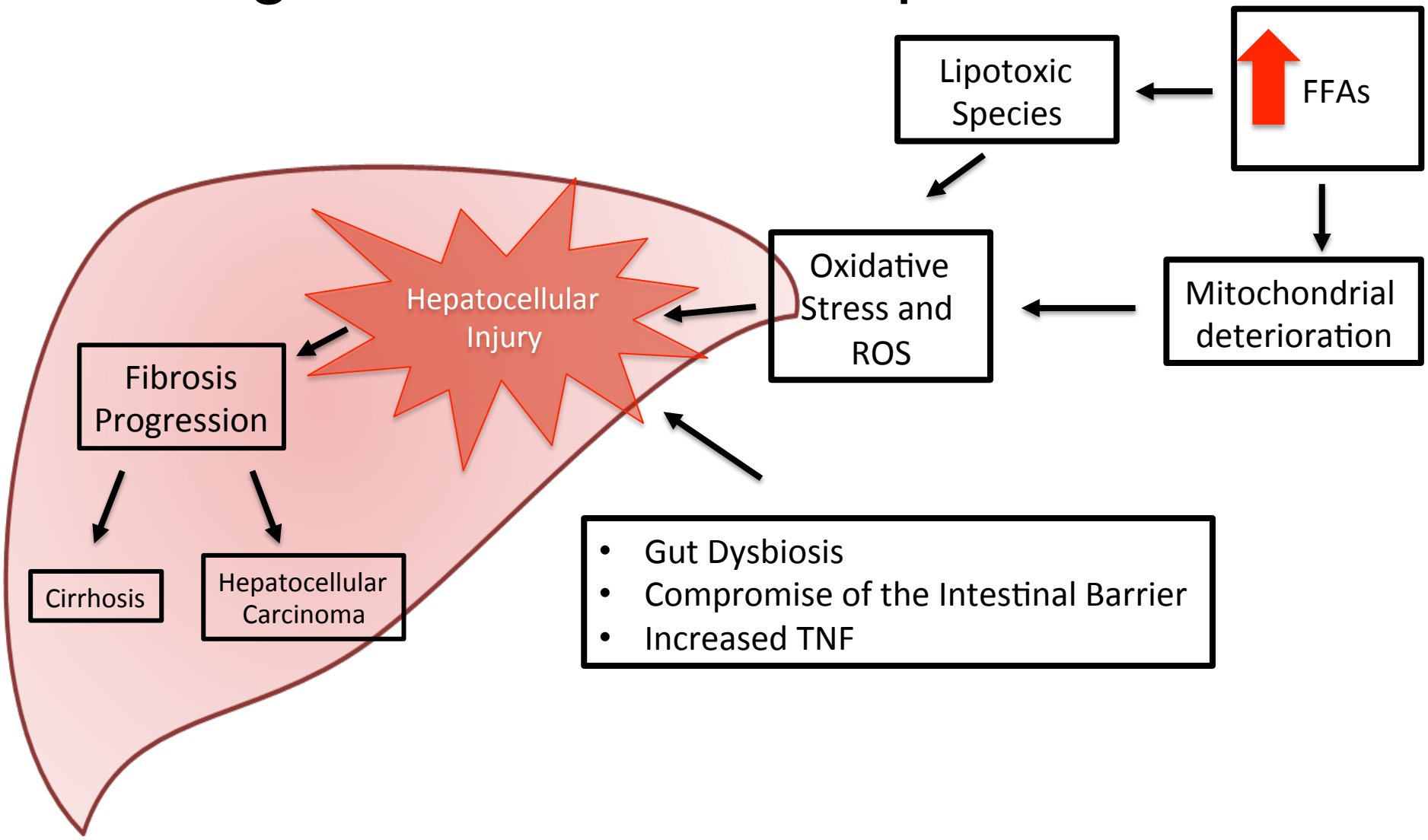
- Risks of increased consumption of fructose:
  - Increase in *de novo* lipogenesis, promotes dyslipidemia, increases visceral adiposity, increases insulin resistance
  - Gut dysbiosis, increased intestinal permeability, increased hepatic inflammation
  - Increased risk of fibrosis in patients with NASH
- Effects of inactivity:
  - Increases body weight, central adiposity, insulin resistance
  - Increases systemic and adipose inflammation
  - Promotes cancer and coronary heart disease

Kistler KD. Am J Hepatol. 2011
Kransoff JB. Hepatology. 2008
Romero-Gomez M. J Hepatol. 2017

Pathogenesis of Hepatic Steatosis:



Pathogenesis of Steatohepatitis:



NAFLD:

Natural History

- Patients with NAFLD likely have increased overall mortality compared to those without:
  - 1.04 HR (Large, international cohort)
- Causes of death:
  1. Cardiovascular: HR 1.46
  2. Cancer
  3. Liver-related

Adams LA. Gastroenterology 2005
Younossi Z. Hepatology 2016
Ekstedt M. Hepatology 2015

NASH:

Natural History

- Increased overall mortality: 2.56 RR
- Increased liver-related mortality: 64.6 RR
- ★ Fibrosis stage predicts mortality in NASH:
  - F0: reference
  - F1-3: 1.82-1.91 HR
  - F4: 6.35 HR

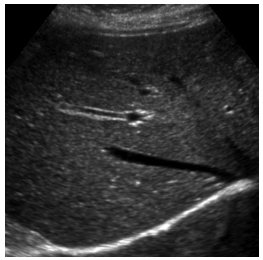
Younossi Z. *Hepatology* 2016
Angulo P. *Gastroenterology* 2015

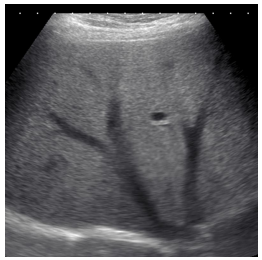
NAFLD:

Diagnosis

- Steatosis seen on imaging performed for other reasons:
  - Ultrasound:
    - "Increased echogenicity" or "Increased echo texture"
    - Excellent sensitivity when steatosis is >30%

Normal Liver





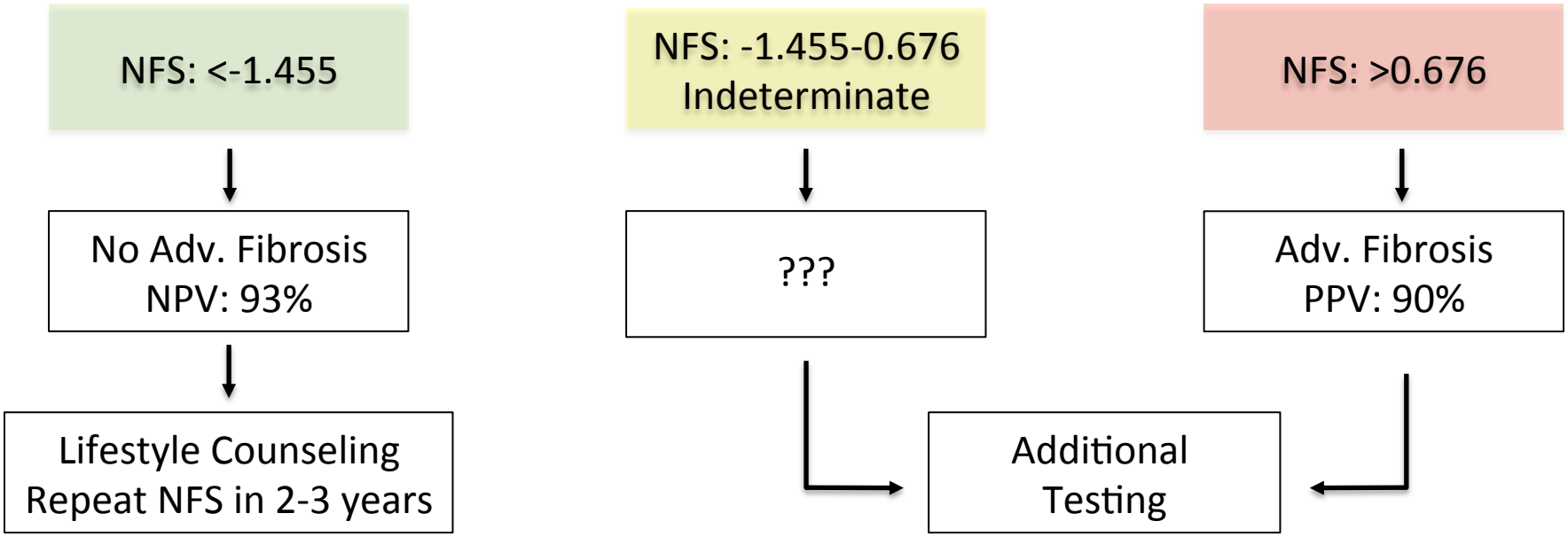
Fatty Liver

  - MRI or Non-contrast CT
- Elevated ALT:
  - 30-60% of patients with NASH have normal ALT
- Symptoms:
  - Usually asymptomatic
  - RUQ fullness or discomfort

Noninvasive Assessment of Fibrosis

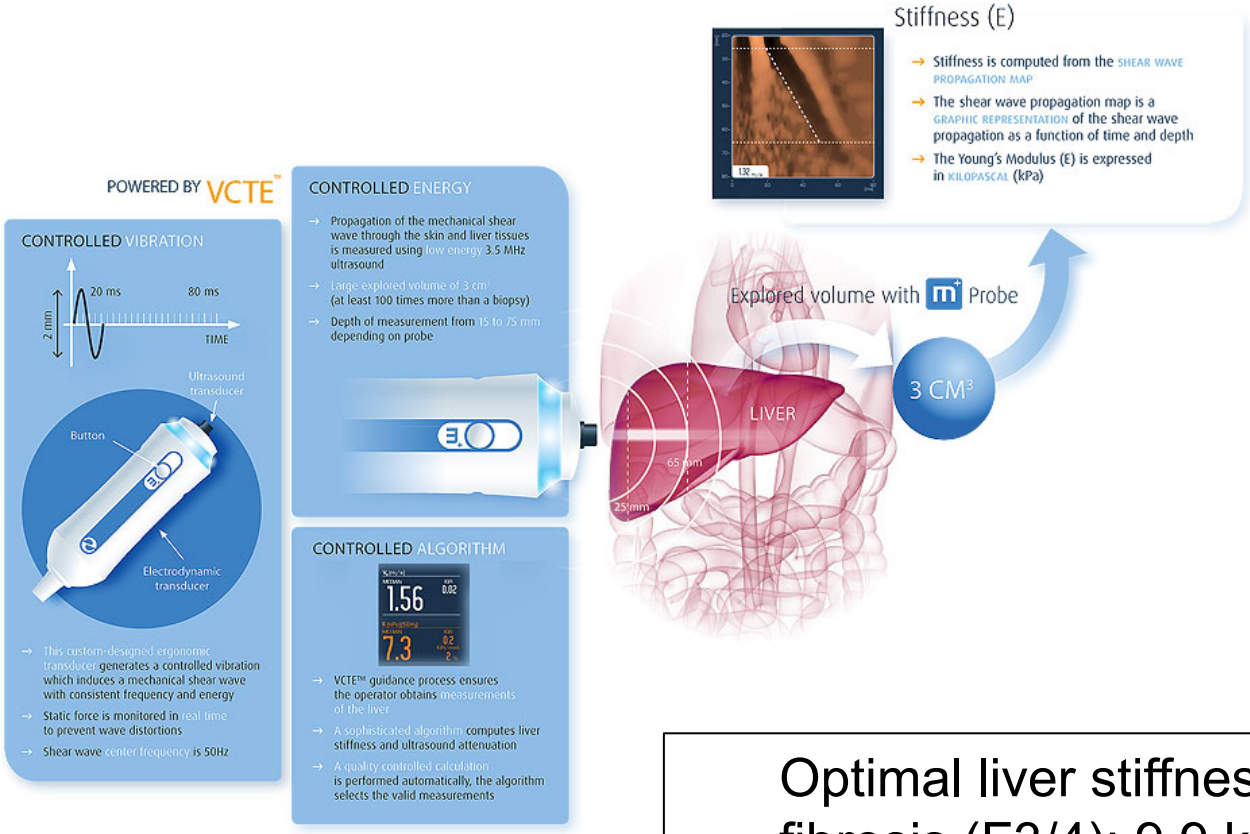
Serum-based tests

- NAFLD fibrosis score (NFS):
  - Age, BMI, Hyperglycemia, Platelet count, Albumin, AST/ALT



Angulo P. Hepatology 2007

Noninvasive Assessment of Fibrosis
Transient Elastography (Fibroscan®)



Valid Test:
- 10 valid measurements
- IQR/median <30%

Test Considerations:
- Must fast for 3 hours
- No Pregnancy
- Falsely elevated with:
  - Active inflammation (ALT >100)
  - Significant Steatosis
  - Hepatic congestion
  - Significant EtOH use

Optimal liver stiffness cutoff for advanced fibrosis (F3/4): 9.9 kPa
95% sensitivity and 77% specificity

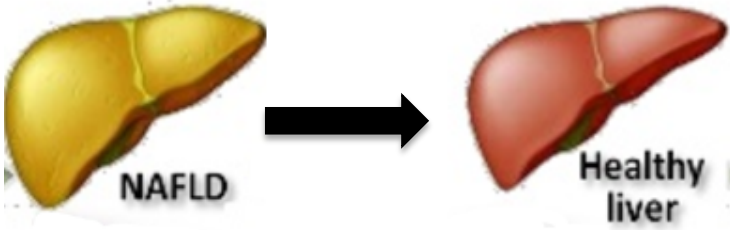
Liver Biopsy:

- When to consider liver biopsy:
  - Patients with risks for NASH and/or advanced fibrosis
    - NFS, Fib4 score, transient elastography, MR elastography
  - Patients at risk for alternative causes of liver disease
- Histopathology:
  - NAFLD activity score (NAS):
    - Grade: necroinflammatory activity
      - Steatosis
      - Ballooning
      - Lobular inflammation
    - Stage: degree of fibrosis
      - F0 (no fibrosis) – F4 (cirrhosis)

Chalasani N. Hepatology 2017

Management of NAFLD:

- NAFLD and NASH *are* REVERSABLE



Management of NAFLD (simple steatosis):

- Screen for the development or worsening of metabolic diseases and treat if indicated:
  - Dyslipidemia, HTN and DMII
- Monitor liver chemistries
- Liver-directed therapy:
  - No proven benefit
- Other therapies:
  - Manage comorbidities
    - **Statins are safe in patients with NAFLD**
  - Lifestyle intervention to achieve weight loss
  - Consider bariatric surgery, if otherwise appropriate

Management of NASH:

- Screen for the development or worsening of metabolic diseases and treat if indicated:
  - Dyslipidemia, HTN and DMII
- Monitor disease progression:
  - Check labs to detect advanced liver disease
- Liver-directed therapy:
  - Consider treatment with pioglitazone or vitamin E
- Other therapies:
  - Manage comorbidities
    - **Statins are safe in patients with NASH**
  - Lifestyle intervention to achieve weight loss
  - Consider bariatric surgery, if otherwise appropriate

Management of NAFLD/NASH:

Lifestyle Intervention

- Modification of diet and physical activity targeted at WEIGHT LOSS

- Goal Weight Loss:
  - 3-5% total body weight (TBW) loss can reverse hepatic steatosis
  - >5-7% TBW loss: can reverse hepatic steatosis and inflammation
  - ≥10% TBW loss: may improve hepatic fibrosis

Musso G. Diabetologia. 2012
Promrat K et al. Hepatology. 2010
Harrison SA et al. Hepatology. 2009

Management of NAFLD/NASH:

Weight Loss

- 52 week intervention of physical activity and calorie restricted diet
  - 30% of patients lost ≥5% TBW
    - 58% had resolution of NASH
    - 82% had a 2-point reduction in NAFLD activity score (NAS)
  - 10% of patients lost ≥10% TBW:
    - 100% had reduction in NAS
    - 90% had resolution of NASH
    - **45% had regression of fibrosis**

Vilar-Gomez *et al.* Gastroenterology. 2015

Management of NAFLD/NASH:

Diet Modification

- Calorie Restriction:
  - 500-750 kcal/day calorie deficit
- Low Carbohydrate versus Low Fat:
  - Similar reductions in hepatic fat with MR spectroscopy
  - Similar reduction in ALT and insulin resistance
- Mediterranean Diet:
  - Beneficial for all-cause mortality, cardiovascular disease, cancer, obesity and DMII
  - Reduces central obesity
  - NAFLD patients: similar weight loss compared to low fat diet, but significant improvement in reduction of hepatic steatosis (MRS) and improvement in insulin sensitivity

Haufe S et al. Hepatology 2011
de Luis et al. Nutr Hosp 2010
Ryan MC. J Hepatol. 2015

Management of NAFLD/NASH:

Physical Activity

- Liver-related benefits of exercise:
  - Improved peripheral insulin sensitivity →Decreased hepatic *de novo* lipogenesis
  - Reduction in visceral fat → Reduction of lipid delivery to the liver
  - Increased hepatic VLDL clearance
- Vigorous Activity in NAFLD:
  - >75 mins/week have a reduced risk of NASH (OR 0.65, CI 0.43-0.98)
  - >150 mins/week have a reduced risk of advanced fibrosis (OR 0.53, CI 0.29-0.97)
- Aerobic exercise *vs.* Anaerobic resistance training:
  - Both reduce hepatic fat content (20-30% relative reduction) independent of weight loss

Romero-Gomez M. J Hepatol. 2017
Kistler KD. Am J Gastroenterol. 2011
Hallsworth K. Gut. 2011

Management of NAFLD/NASH:

Weight Loss

- Effectiveness of weight loss as a therapeutic intervention:
  - Weight loss success:
    - <50% of patients in these trials were able to lose 5-7% of their body weight
  - Weight loss sustainability:
    - Half of the initial weight loss is typically regained within the first 3 years
    - Similar amount of weight regain within 3 years whether weight loss is rapid or gradual

Musso et al. Diabetologia. 2012

Benefits of Bariatric Surgery:

- Weight reduction:
  - 10 years: sustained 14-25% total body weight loss
- Improvement/remission:
  - DMII: 75% at 2 years
  - HTN: 70-79% at 1 year
  - HL: 60-100% of patients no longer require lipid lowering medication
  - Cardiovascular death
  - Overall mortality

Shouhed D. Expert Rev of Gastro Hepatol. 2017
Pontiroli AE. Ann Surg. 2011

Management of NAFLD/NASH:

Bariatric Surgery

- Lassailly *et al.* 2015:
  - Prospective study; N=109 patients with NASH
  - Paired Bx: before and 1 year post- surgery:
    - BMI: 49 → 37
    - NASH resolution: 85%
    - Fibrosis regression: 34%
- AASLD Guidelines, 2017:
  - Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH.
  - It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.

Pharmacologic Treatment of NASH:

Vitamin E

- Anti-oxidant to alleviate the oxidative stress associated with NASH pathophysiology

- The PIVENS trial (NEJM 2010); non-diabetics:
  - 42% had significant improvement in NAS vs.19% in placebo at 24 months (p=0.001)
  - No improvement in fibrosis score (p= 0.24)

- Adverse side effects:
  - Long-term use is associated with increased risk of prostate cancer and hemorrhagic stroke

Sanyal AJ. NEJM. 2010
Klein EA. JAMA. 2011

Pharmacologic Treatment of NASH:

Pioglitazone

- PPAR agonist: reverses adipose tissue dysfunction and insulin resistance in obesity and DMII
- Cusi K *et al* 2106; prospective, RCT, preDM/DMII:
  - 58% had significant improvement in NAS vs. 17% placebo
  - 51% had significant resolution of NASH vs. 19% placebo
  - 39% had improvement in fibrosis vs. 25% placebo
- Musso G *et al*; Meta-analysis of NASH patients with advanced fibrosis (F3-4) treated with pioglitazone:
  - Primary outcome: improvement in fibrosis stage from F3-4 to F0-2
  - Results:
    - OR 3.15 (1.25-7.93) for improved fibrosis
    - OR 3.22 (2.17-4.79) for NASH resolution

Musso G et al. JAMA Intern Med 2017
Cusi K. JAMA Int Med. 2016

Pharmacologic Treatment of NASH:

Pioglitazone

- Adverse side effects:
  - Weight gain (2.5-4.7kg) in clinical trials
  - May promote bone loss in women

Musso G et al. JAMA Intern Med 2017

Non-Alcoholic Fatty Liver Disease:

Key Points

- Most common cause of chronic liver disease in the developed world
- Slated to be the primary indication for liver transplantation in the next decade
- NAFLD is associated with increased overall mortality
  - Primarily from cardiovascular death
- Advanced fibrosis predicts overall and liver-related mortality in patients with NASH

Non-Alcoholic Fatty Liver Disease:

Key Points

- Weight loss through lifestyle modification is the most effective therapy for NAFLD
- Goal Weight Loss:
  - ★ ≥10% associated with improved fibrosis
- Diet Modification:
  - Calorie restriction (500-750 kcal/day deficit)
  - Limit industrial fructose intake
- Increase Physical Activity:
  - Benefits independent of weight loss
  - Helps maintain weight loss

Non-Alcoholic Fatty Liver Disease:

Key Points

- Bariatric Surgery:
  - Well-designed, large, prospective RCTs are lacking
  - Improves/reverses steatosis, inflammation and fibrosis in NASH
  - **Insufficient data to recommend as primary therapy for NAFLD/NASH**
- Pharmacologic Treatment of biopsy proven NASH:
  - Consider vitamin E (800 IU/day alpha tocopherol) in nondiabetics
  - Consider pioglitazone in patients with or without DMII after discussion of potential side effects