Nonalcoholic fatty liver disease (NAFLD)
Nonalcoholic steatohepatitis (NASH)

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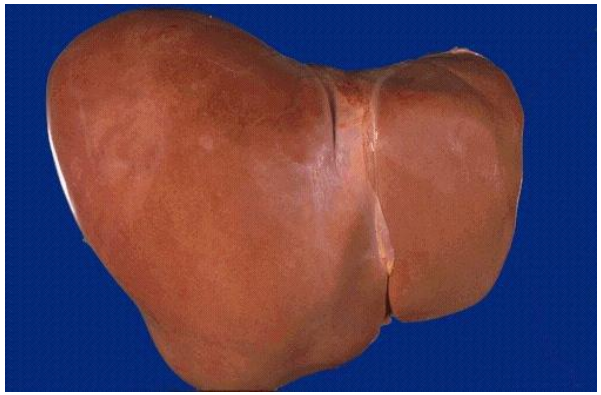


Disclosure of Financial Relationships

Dawn M. Torres, MD

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Research Grants/Contracts

Abbvie, Galectin, Gilead, Intercept, Conatus

Speaker's Bureau

None

Objectives

- Describe the primary etiologies of chronic hepatitis today and predictions for the future face of liver disease
- Understand the criteria required for the diagnosis of NAFLD and NASH
- Outline the current available treatments for NAFLD and NASH

QUESTION

What is the most common chronic liver disease in the US?

A) Chronic hepatitis C
B) Autoimmune hepatitis
C) Chronic hepatitis B
D) Non-alcoholic fatty liver disease
E) Drug induced liver disease

ANSWER

- D) Non-alcoholic fatty liver disease

- Most common cause of liver disease globally. In U.S. prevalence is estimated at 30-40%

Case #1: 55 year old Hispanic female

- **- ROS:** N/V/F/C. Occasional vague RUQ pain not assoc w/meals, BMs. No diarrhea, constipation, blood in stool.
- **+ ROS:** 20 lbs wt gain over 5 years
- **PMH:** DM Type 2, HTN, HLD, OSA, GERD
- **PSH:** Lap chole 2010 & TAH Hysterectomy 2005
- **Soc:** 1-2 drinks per week, no tobacco
- **Family History:** Grandmother with cirrhosis
- **Meds:** Metformin, Lisinopril/HCTZ, Atorvastatin, Aspirin, Prilosec

Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- **Physical exam:** HR 86, BP 137/80, RR 12, SPO2=98% RA, T 98.4, BMI 32.5
- Gen: Obese Hispanic female in NAD, A/Ox3, conversant & cooperative
- Lungs: CTA
- Cardio: RRR
- Abd: obese with well healed surgical scars. Liver palpable 3 cm below costal margin, spleen nonpalpable, nontender
- Extremities: no stigmata of liver disease, no pedal edema, no rashes

Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- **Basic labs:**
- CBC: WBC 7, HCT 39, platelets 150
- INR 1.0
- Alk phos 80 AST 52 ALT 74   T bili 0.4
- TP 7.8, Albumin 3.9

Case #1: 55 year old Hispanic female

- **Helpful additional information:**
  - **Duration of liver enzyme elevation**
  - **Supplements or herbals**
  - **Risk factors for viral hepatitis – tattoos, IVDU or intra-nasal cocaine, high risk sexual behavior (anal intercourse, multiple partners), blood tranfusion 1990s or earlier**
  - **Etiology of cirrhosis of grandmother**
  - **Health care maintenance: colonoscopy, pap/mammogram**

Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- **What is your differential diagnosis?**
- **What labs and imaging studies should be ordered?**
- **Is a liver biopsy indicated?**

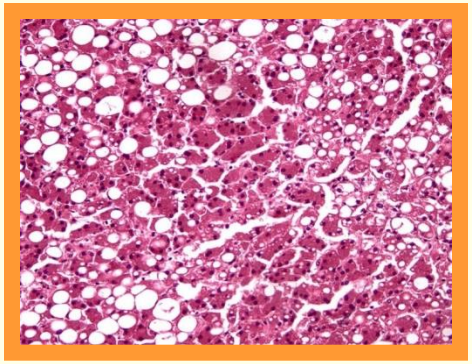
Differential diagnosis: asymptomatic mild-moderate hepatocellular liver enzyme elevation

- NAFLD
- Alcohol related liver disease
- Viral Hepatitis (B, C)
- Autoimmune hepatitis
- Drug induced liver injury
- Hemochromatosis
- Alpha-one anti-trypsin deficiency
- Thyroid dysfunction, Celiac

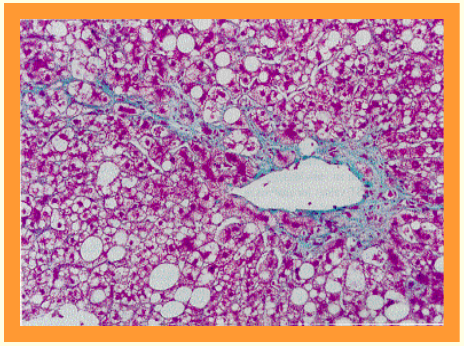
Case 1: Additional information

- Hgb A1c 7.5
- Hep C Antibody negative
- Hep B core Ab neg, surface Ag neg, surface antibody positive
- ANA neg, IgG normal
- TTG negative, total IgA normal
- TSH normal
- Ferritin & iron panel normal
- RUQ US with hepatic steatosis

Non-alcoholic fatty liver disease: Basic definitions



All pts with fatty liver



Liver biopsy

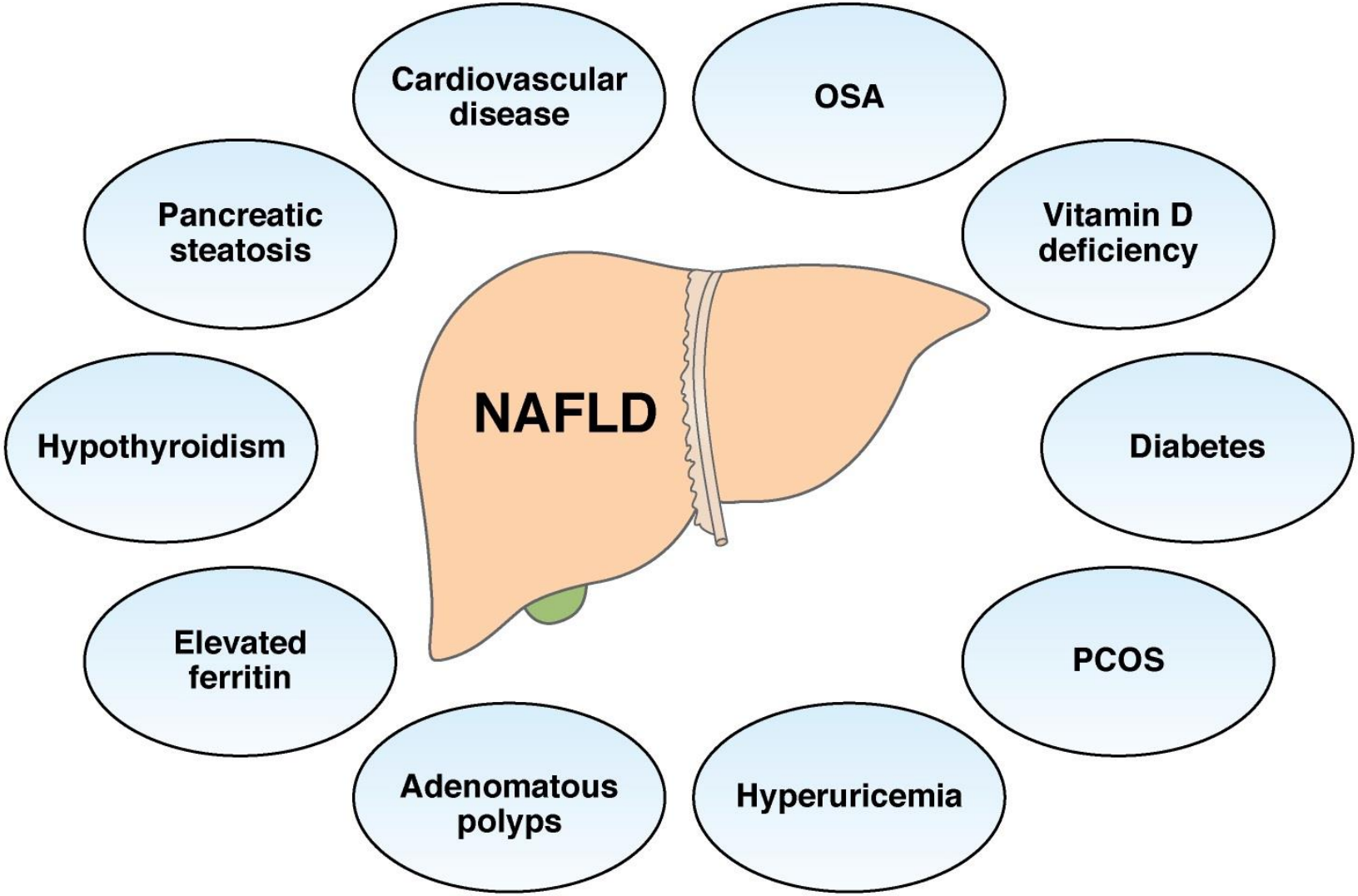
Isolated fatty liver

Non-alcoholic steatohepatitis (NASH): fat + inflammation +/- fibrosis

Increased risk: Cirrhosis & Liver cancer

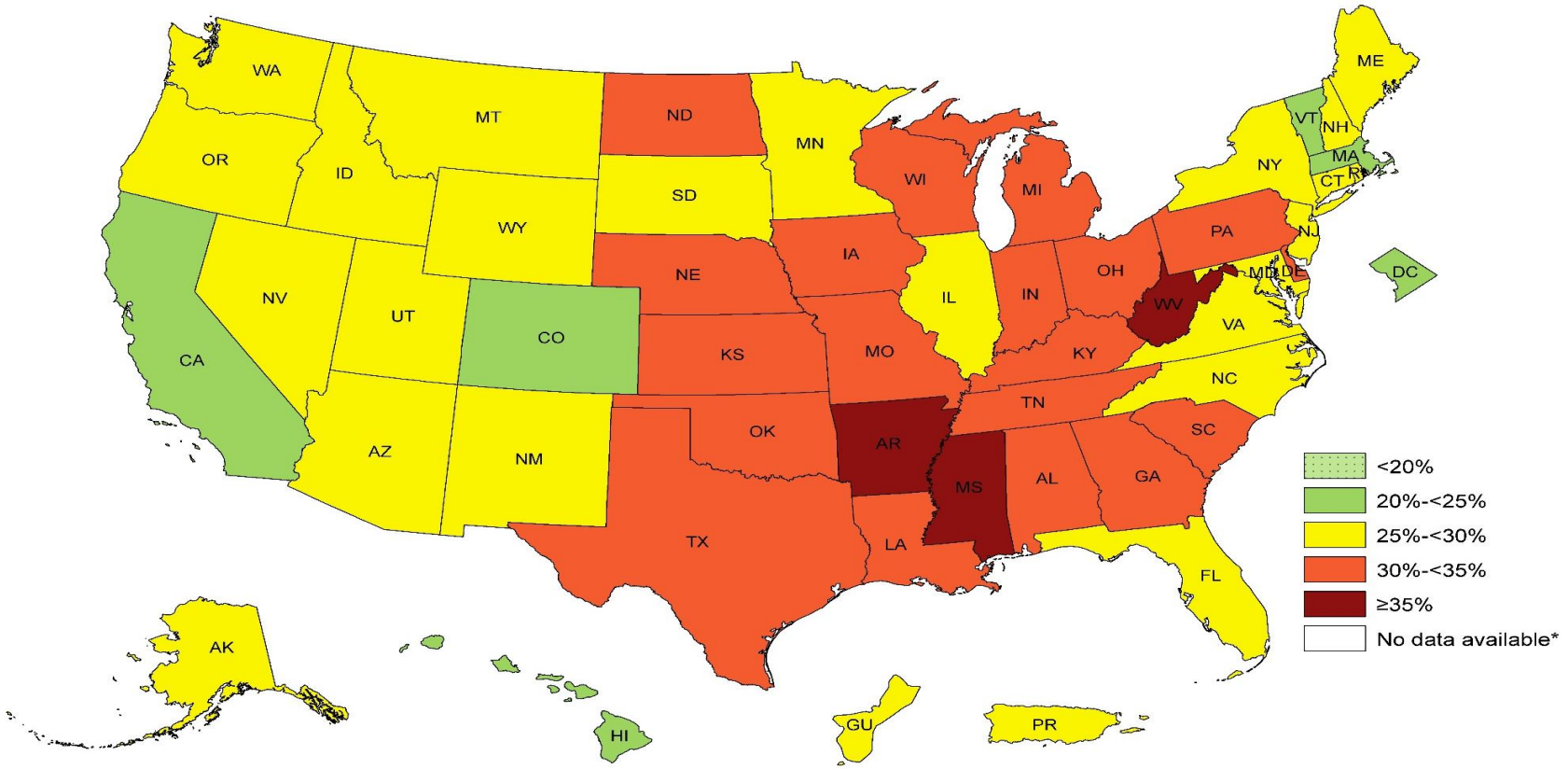
**Alcoholic steatohepatitis (ASH) cannot be differentiated from NASH on biopsy, history is critical

NAFLD Clinical Associations

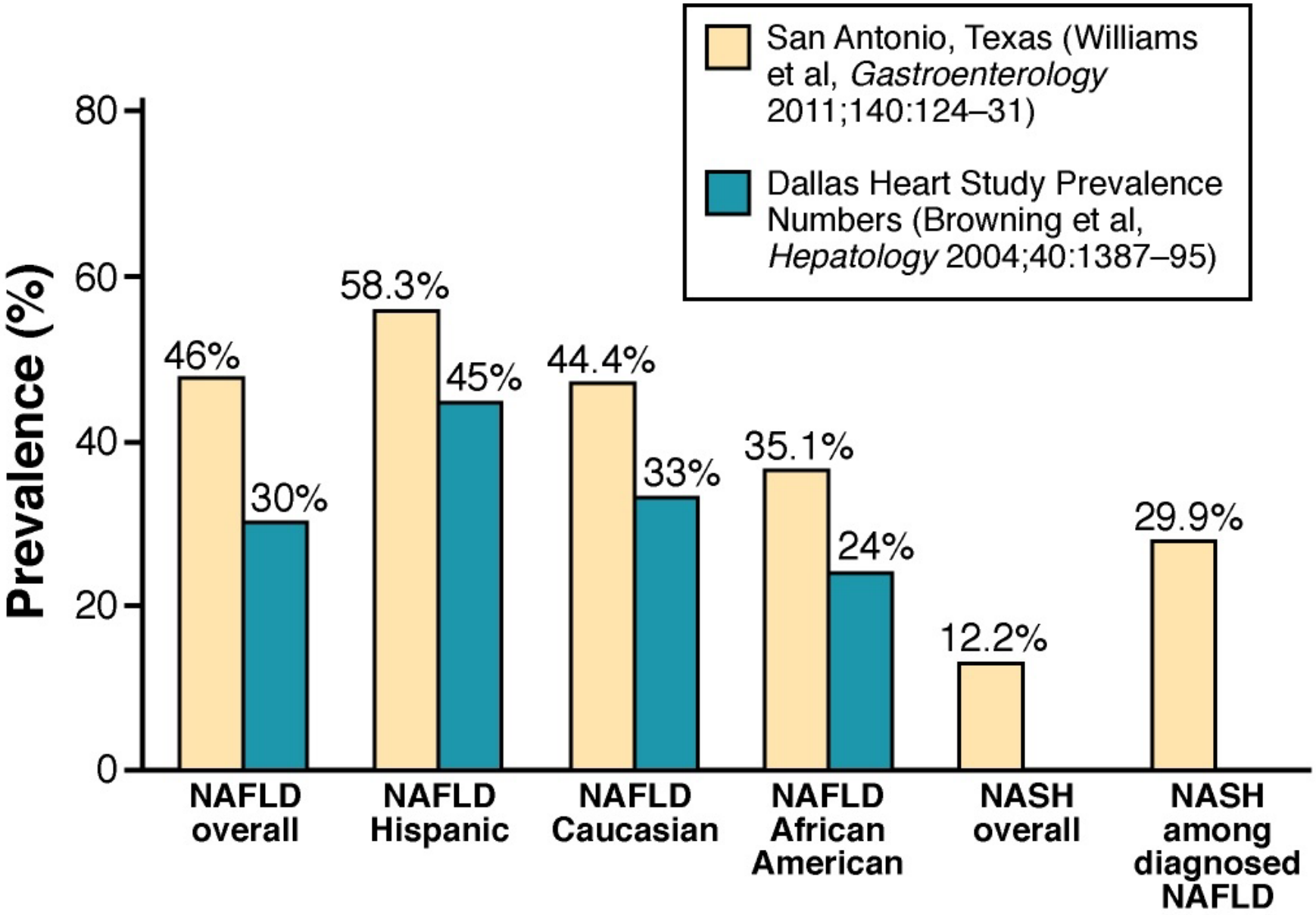


Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of NAFLD. Clin Gastro Hepatol 2012.

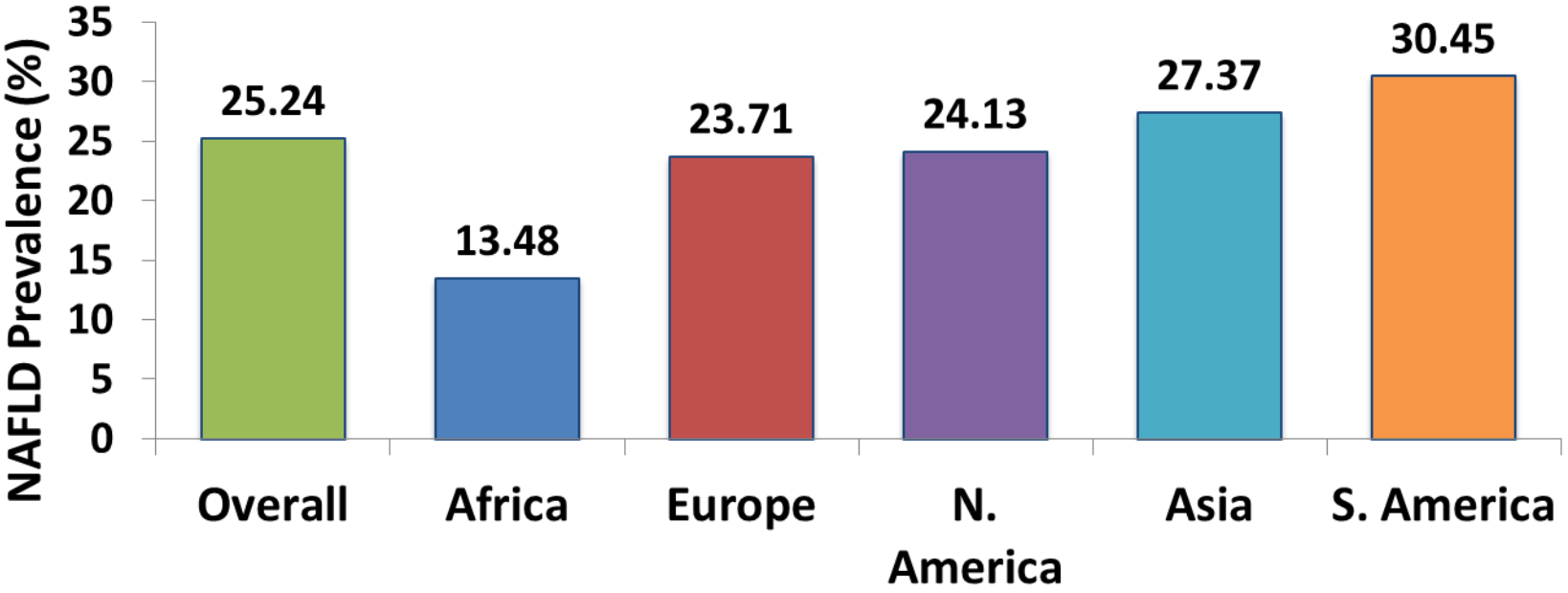
Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory 2014



NAFLD Prevalence



Global Epidemiology of NAFLD

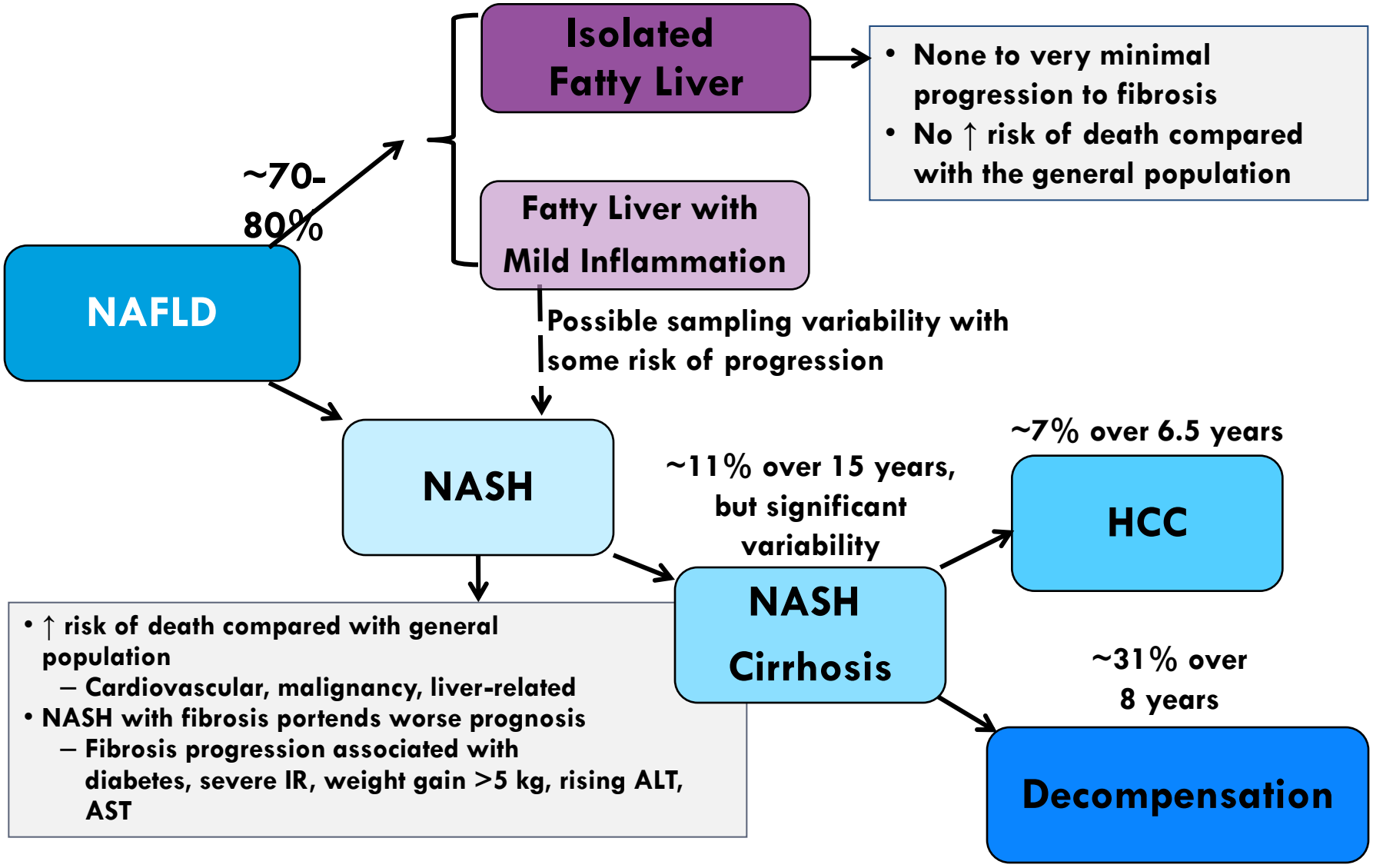


Systematic literature search

- 729 studies evaluated, 86 studies included
- 57 studies analysed NAFLD prevalence, 15 studies analysed for NASH prevalence

Abbreviations: N, North; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; S, South.
Younossi ZM, et al. *Hepatology.* 2016;64:73-84

Natural History of NAFLD



With permission from Torres DM, et al. *Clin Gastroenterol Hepatol*. 2012;10:837-858.

High risk patients

- Diabetic
- Hispanic
- BMI>28
- AST/ALT ratio ≥ 0.8
- Co-existing liver disease
  - Alcohol use
  - Hepatitis C

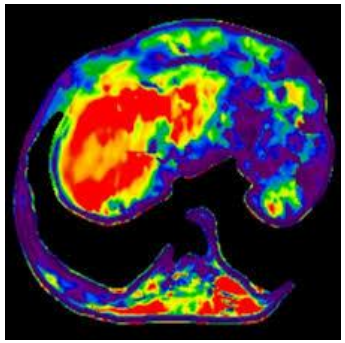
Who to biopsy?

- Diagnostic dilemma
- High risk
  - Non-invasive risk stratification
    - NAFLD fibrosis score, BARD score, etc
    - Fibroscan, MR Elastography, etc
- Failed lifestyle modification

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)
BMI (kg/m²)
IGF/diabetes ☐
AST
ALT
Platelets (x10⁹/l)
Albumin (g/l)
calculate score



Noninvasive Tests for Liver Fibrosis

- Clinical or laboratory tests
  - NAFLD Fibrosis Score
  - FIB-4 index
  - BARD
  - AST/ALT ratio
- Imaging modalities
  - Shear-wave elastography
    - Fibroscan, Supersonic imaging, ARFI
    - MRE
  - MRI-based
    - Liver MultiScan

Abbreviations: ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease.

NAFLD fibrosis score

Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
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Age (years)

BMI (kg/m²)

IGF/diabetes ☐

AST

ALT

Platelets (x10⁹/l)

Albumin (g/l)

calculate score

http://nafldscore.com

$-1.675 + (0.037 \times \text{age[years]}) + (0.094 \times \text{BMI [kg/m}^2\text{]}) + (1.13 \times \text{IFG/diabetes [yes = 1, no = 0]}) + (0.99 \times \text{AST/ALT ratio}) - (0.013 \times \text{platelet[10}^9\text{/L]}) - (0.66 \times \text{albumin[g/dL]})$

NAFLD Fibrosis Score

- Derivation and validation of the scoring system
- 733 NAFLD patients: 480 derivation; 253 validation
- Multivariate analysis
  - Age, hyperglycemia, BMI, platelet count, albumin, AST/ALT ratio → independent predictors of advanced fibrosis

Cutoff Point	Group	Predictive Value for Advanced Fibrosis
Low cutoff point: <–1.455	Derivation	NPV 93%
	Validation	NPV 88%
High cutoff point: >0.676	Derivation	PPV 90%
	Validation	PPV 82%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value.

Angulo P, et al. *Hepatology.* 2007;45:846-854.

Transient Elastography

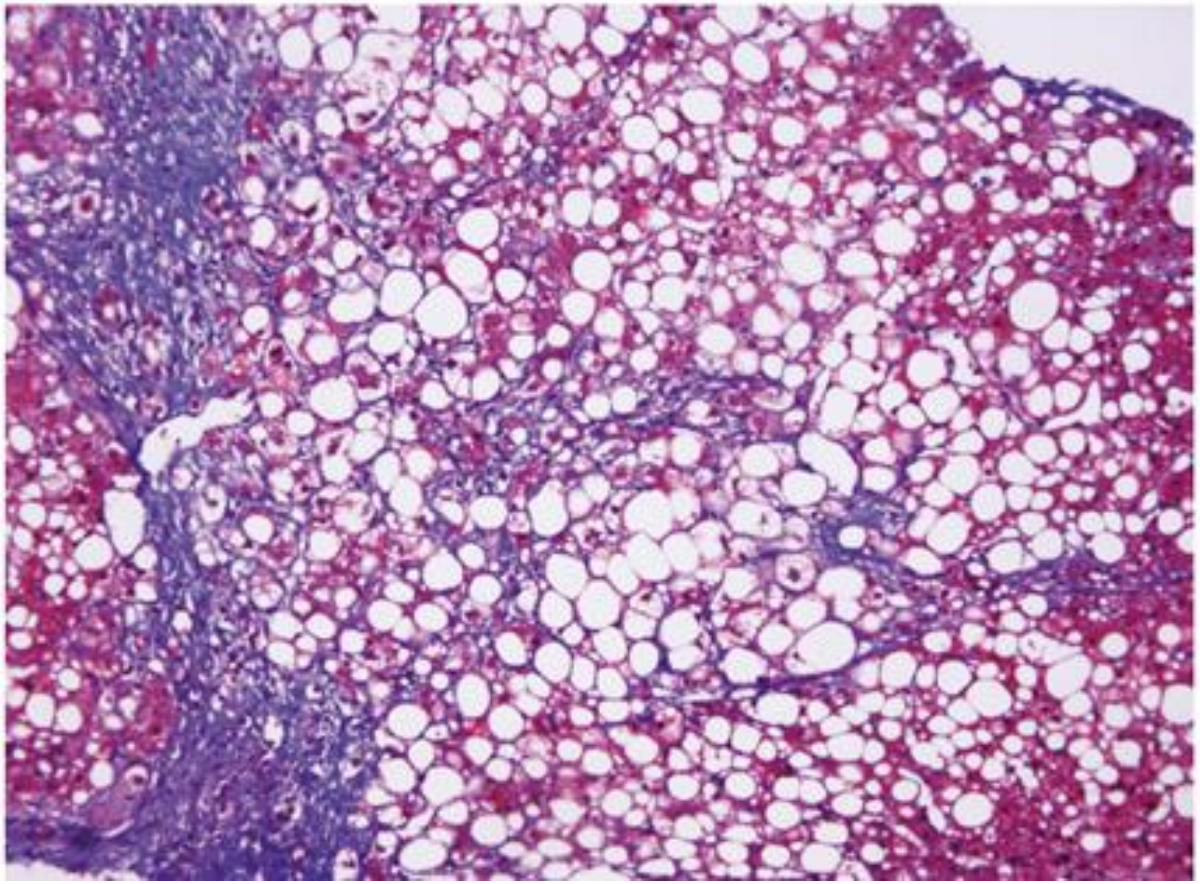
- FibroScan® = patented technology **V**ibration **C**ontrolled **T**ransient **E**lastography (VCTE™)
- Two quantitative parameters:
  - Liver stiffness expressed in kPa
    - ➔ Correlated to liver fibrosis [1]
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    - ➔ Correlated to liver steatosis [2]
- Volume of liver tissue (3cm^3)
  - 100 times bigger than liver biopsy

FibroScan® 502 TOUCH

Case 1: Additional information

- **NAFLD fibrosis score:** 2.00
  - <-1.455 predicts F0-1 fibrosis
  - <-1.455 to <0.675 indeterminate
  - >0.675 predicts significant fibrosis
- **Fibroscan:** 9 kPascals

Liver biopsy: Stage 3 NASH

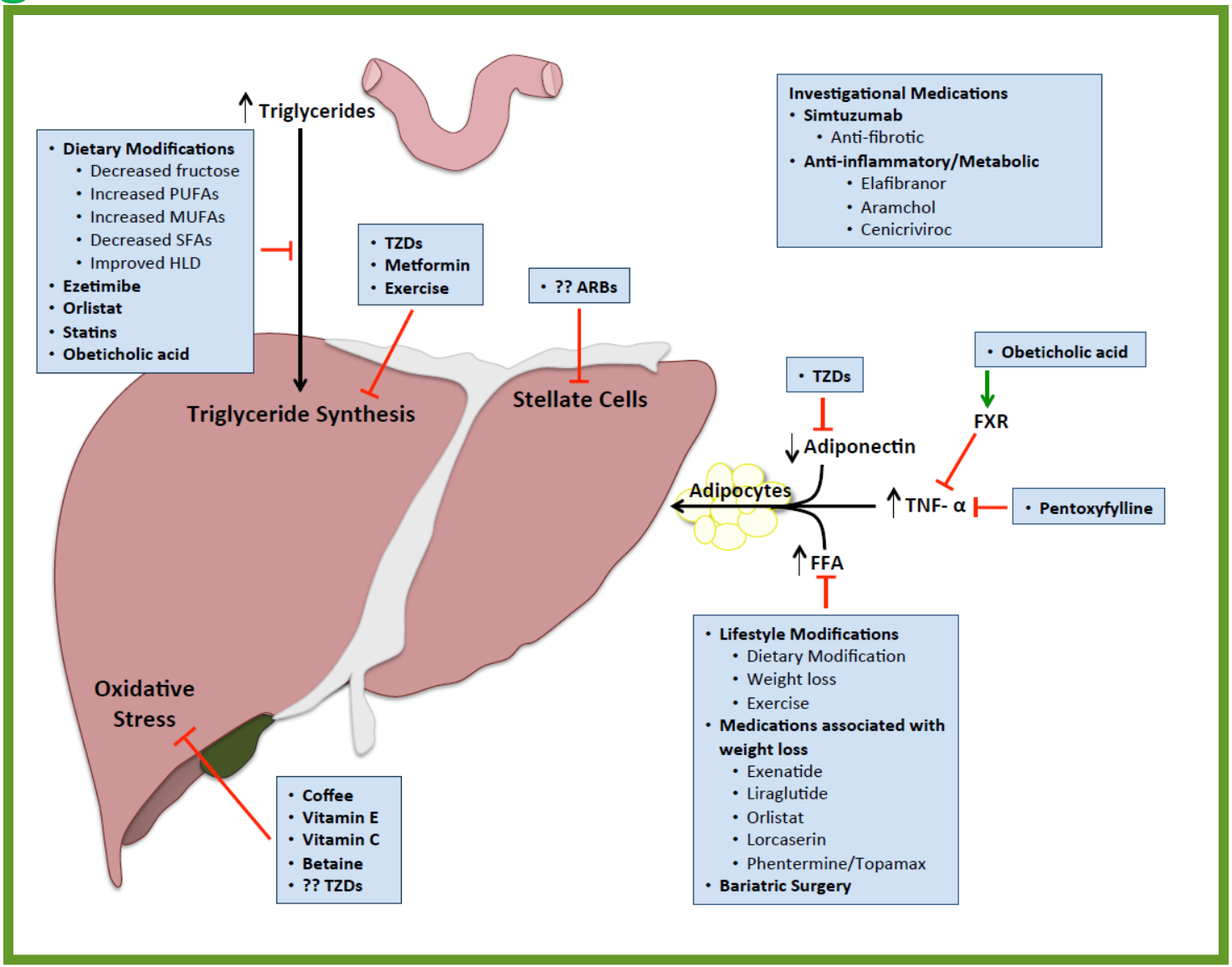


http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0120-99572014000100012&lng=pt&nrm=iso&tlng=en

Case 1: Stage 3 NASH…Now what?

- What is the optimal treatment for NAFLD patients?
  - **Diet/exercise**
  - Surgical
  - Pharmacotherapy

Pathogenesis of NASH with Potential Sites for Therapy



Pence M, Stratton A, Torres DM et al. 2016 *in press.*

NAFLD: Dietary Characteristics

- ↑ saturated fat/cholesterol [1]
- ↓ polyunsaturated fat, fiber, antioxidant vitamins C & E[1]
- ↑ intake soft drinks & meat; ↓ omega -3 fatty acids [2]
- ↑ net energy intake[3]
- High fructose diets may also contribute to NAFLD[4]

1. **Musso G et al, *Hepatology.* 2003;**
2. **2. Zelber-Sagi S, J Hepatol 2007**
3. **3. Capristo E, *Euro Rev Med Pharmacol Sci.* 2005**
4. **4. Ackerman Z et al, *Hypertension.* 2005**

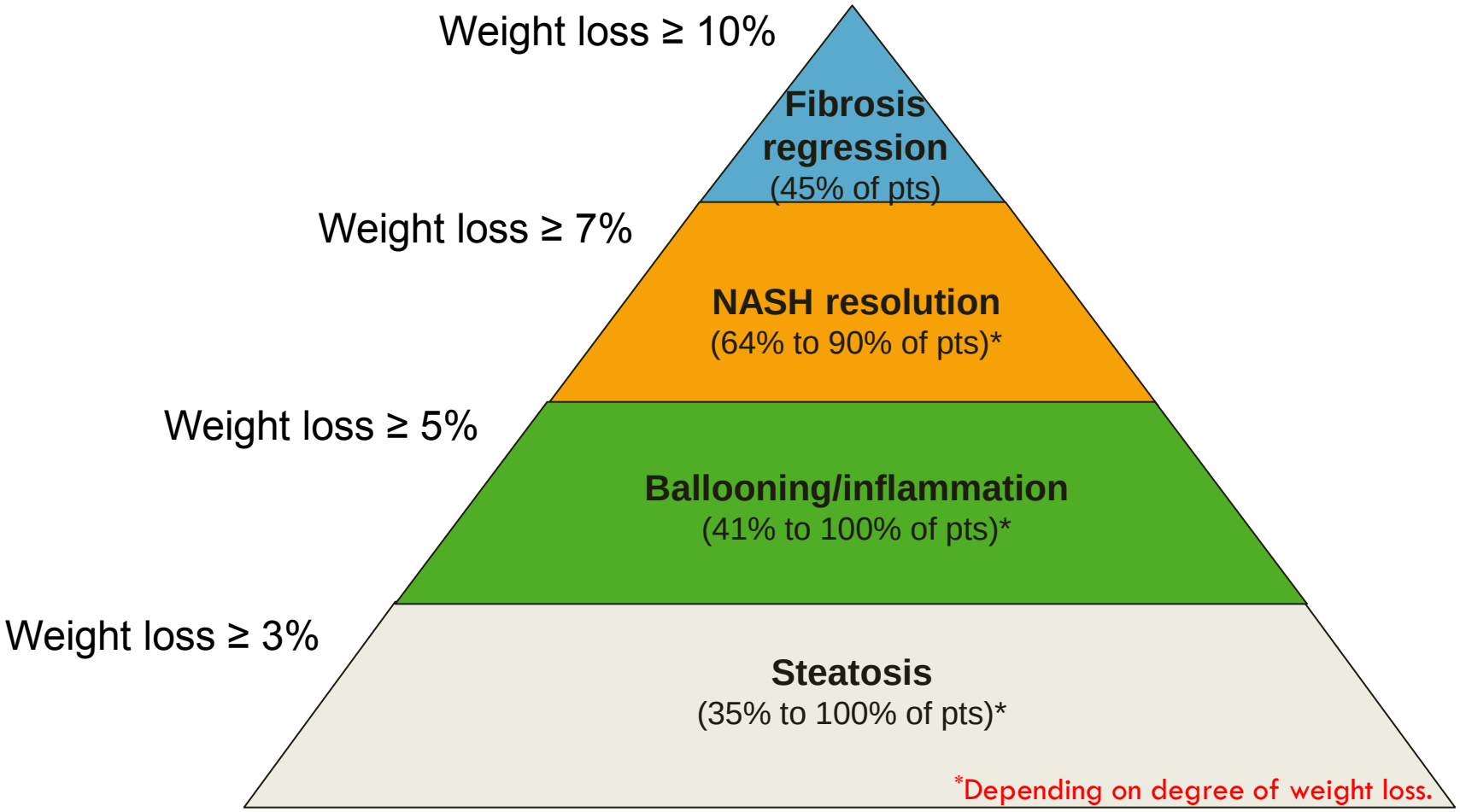
Weight Loss

- Effective
  - 9-10% body weight loss
    - improved insulin sensitivity, liver enzymes, hepatic steatosis, ballooning degeneration, & lobular inflammation
- Sustainability??
  - 1310 patients lost 10% weight 1999-2002 NHANES study
  - 66.5% maintained or reduced weight
    - Sedentary lifestyle → inability to maintain weight loss

Weiss EC et al. Am J Prev Med 2007;33:34-40

Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies



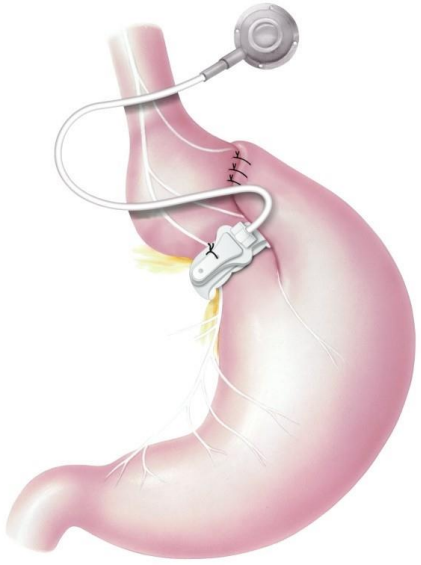
Hannah WN, et al. Clin Liver Dis. 2016;20:339-350.

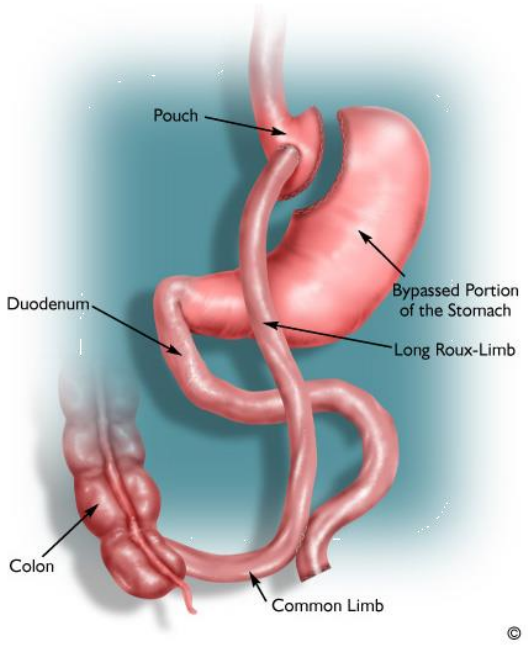
Exercise

- Moderate exercise, expending 400-kcal/session, 3 times/week → ↑insulin sensitivity
- Overall energy expenditure achieved per work-out more important than intensity
- Aerobic or resistance training both of benefit

Bariatric Surgery

- Duodenal switch procedure
- Adjustable gastric banding
- Roux-en-Y gastric bypass
- Gastric sleeve





Bariatric Surgery for Adult NAFLD

Study	Type of Surgery	Mean WT Δ	Steatosis Improvement	Pericellular Fibrosis Change	Hepatocellular Injury	NASH Resolved	Histopathologic Worsening
Dixon et al [68]	LAGB	34 kg	Significant (p<0.001)	91% improvement; 70% resolution	100%	82%	None
de Almeida et al [73]	RYGBP	22.3 kg	75% resolution	50% improvement	69% resolution	94%	None
Barker et al[72]	RYGBP	18 kg	100%	47% improvement	Improvement (p<0.001)	89%	10.5% mild fibrosis increase
Mattar et al[71]	RYGBP (41) LSG (23)	46.8 kg	37% complete resolution	20% complete fibrosis resolution	NA	NA	None
Mathurin et al[69]	BIB, LAGB	27 kg	Significant p<0.0001	0.14 to 0.38 (p=0.0001)	NA	75%	Mild fibrosis ↑ 1 year
Mottin et al[75]	RYGBP (Majority)	NA	82.2% (54% resolution)	NA	NA	NA	None
et al[74]	RYGBP	53.7 kg	81% resolution	43%	86%	81%	None
Furuya et al [70]	RYGBP	19.3 kg	84% resolution	75% resolved fibrosis	50%	No pts NAS of >4	None
Liu X et al [76]	RYGBP	50.2 kg	97% resolved macrosteatosis	Fibrosis ↓: 50% → 25%	100%	100%	2.5% mild fibrosis
Kral et al[67]	BPD	38 kg	↓ grade 1.57 to 0.52 (p<0.0001)	Severe 27%; mild 40%	NA	NA	Mild fibrosis ↑over > 3 years
Csendes et al[77]	RYGBP	15.7 kg	93%	4/5 (80%)	5/5 (100%)	100%	6.7% (mild)

Modified from Kashi M, Torres DM, Harrison. Seminars in Liver Disease 2008.

Bariatric Surgery

- **Newer procedures improve NASH histology**
- **Consider if comorbid conditions that would warrant morbidity/mortality of surgery**

Pharmacotherapy

- Weight loss medications
- Insulin sensitizers/diabetic medications
- Anti-oxidants
- Anti-fibrotic agents

Weight loss meds

- Orlistat
  - Reversible inhibitor of gastric & pancreatic lipase
  - Blocks 30% of fat absorption
- 5-10% ↓ body weight w/6-12 months tx
- Pilot trials show benefit but related to wt loss not orlistat
- Others not studied
  - Phentermine/topamax
  - Lorcaserin

Kim W et al. Pharmocological Reviews 2008;60,470-497.

Diabetic medications

- Thiazolinediones (TZDs)
  - Avandia
  - Actos
- Metformin
- Incretin mimetics

Pioglitazone

- Thiazolidinedione (TZD) = selective peroxisome proliferator-activated receptor-gamma agonist
- ↑ insulin sensitivity
  - adipose tissue, muscle, liver
- Approved for diabetes treatment
- Well studied in NASH

Major studies with histologic endpoints

Author, Year, Name	Length	Dosing	N (Tx + Placebo)	Results
Belfort 2006	6 months	Pioglitazone 45 mg/d	26+21	Pioglitazone ↓ fibrosis & inflammation not placebo
Ratziu 2008 (FLIRT)	12 months	Rosiglitazone 4mg/d →8 mg/d	32+31	Rosiglitazone ↓ steatosis but not fibrosis, ballooning, inflammation
Aithal 2008	12 months	Pioglitazone 30 mg/d	37+37	Pioglitazone ↓ fibrosis, injury more than placebo but not steatosis, inflammation
Sanyal 2010 (PIVENS)	96 weeks	Pioglitazone 30 mg/d	80+83	Pioglitazone no better than placebo for fibrosis, NAS but did resolve NASH>placebo (or Vit E)

Modified from: Singh S et al.. Hepatology 2015.

Pioglitazone

- The pro's
  - ↓ insulin resistance
  - Improves hepatic histology albeit modest fibrosis benefit
  - Previous concerns of bladder cancer likely unwarranted[1]
- The con's
  - Weight gain (5-10 pounds)
  - Bone fractures in diabetics[2]
  - CHF Black box warning (rare)
  - Benefits short-lived after discontinuation of therapy

[1] Levin D et al. Diabetologia 2015;58:493-504.
[2] Aubert RE et al. Diabetes Obes Metab 2010;12:716-721.

Pioglitazone

- **Tri-society guidelines (AASLD, ACG, AGA):**
  - **Pioglitazone can be used to treat steatohepatitis in biopsy proven NASH patients. However it should be noted that the majority of the patients used in clinical trials were non-diabetic and long term safety/efficacy is not established for NASH[1]**
- **Consider in diabetic NASH patients without heart failure who can tolerate modest weight gain**

[1]Chalasani N et al. Gastroenterology 2012;142:1592-1609.

Metformin

- Biguanide improves insulin sensitivity
  - Decreases hepatic gluconeogenesis
  - Limits triacylglycerol production
- Promising animal studies
- Adult & pediatric NAFLD
  - improves hepatic steatosis
  - no significant improvement in fibrosis & necroinflammation

Incretin mimetics and enhancers

- Intestinal glucose load → activation of GIP and glucagon-like peptide (GLP-1) → insulin secretion
  - Pathway deficient in type 2 diabetes
- 2 types:
  - Direct GLP-1 mimetic
    - Exenatide
  - DPP-4 inhibitors
    - Sitagliptin
    - Vildagliptin
- Some benefits in animal/pilot studies
- Need more data

Kim W et al. Pharmocological Reviews 2008;60,470-497.

Vitamin E

- Free radical scavenger & antioxidant
- Multiple RCTs with variable endpoints
- Liver associated enzymes improve
  - Meta-analysis 4 NAFLD studies[1]
    - AST ↓ 19.43 U/L and ALT ↓ 28.91 U/L

[1]Sato K et al. Nutrition 2015;31:923-930

Major studies with histologic endpoints

Author, Year, Name	Length	Dosing	N (Tx + Placebo)	Results
Harrison 2003	6 months	Vit E 1000 IU/d & Vit C 1000 mg/d	25+24	Vit E/C superior to placebo for fibrosis score but NOT inflammation/necrosis
Sanyal 2010 (PIVENS)	96 weeks	Vit E 800 IU/d	84+83	Vit E improved ballooning, NAS, no Δ fibrosis
Lavine 2011 (TONIC)	96 weeks	Vit E 800 IU/d	58+58	Vit E improved NAS, induced resolution of NASH (58% v 28%)

Modified from: Singh S et al. Hepatology 2015.

Meta-analysis Vitamin E versus placebo

Parameter	Risk Ratio (95% CI)
Fibrosis	0.93 (0.79, 1.09)
Ballooning degeneration	0.73 (0.61, 0.81)
Steatosis	0.73 (0.59, 0.89)
Lobular Inflammation	0.82 (0.62, 1.09)

Modified from: Singh S et al. Hepatology 2015.

Vitamin E Potential Risks

- ? ↑ all-cause mortality with high dose Vit E [1, 2]
- 400 IU/day ↑ risk prostate cancer [3]
  - Absolute increase 1.6 per 1000 person yr of Vit E use

[1]Miller ER 3rd et al. Ann Int Med 2005;142:37-46.
[2]Bjelakovic G et al. JAMA 2007;297:842-57.
[3]Klein EA et al. JAMA 2011;306,1549-56.

Vitamin E

- Tri-society guidelines (AASLD, ACG, AGA) recommend Vit E for non-diabetic NASH patients[1]
- Reasonable to consider Vit E 400-800 IU once daily for non-diabetic NASH patients

[1]Chalasani N et al. Gastroenterology 2012;142:1592-1609.

Pentoxyfylline

- Nonspecific phosphodiesterase inhibitor shown to ↓ TNF-α
- Used to treat claudication
- Has been studied in NASH[1]

[1]Li W et al. Lipids Health Dis 2011;10:49.

Pentoxyfylline (PTX)

Author, Year, Name	Length	Dosing	N (Tx + Placebo)	Results
Van Wagner 2011	12 months	PTX 400 TID	21+9	PTX improved NAS but not superior to placebo in resolving NASH (44% v 28%)
Zein 2011	12 months	PTX 400 TID	26+29	PTX improved NAS by 2 pts (38.5% v 13.8%) and resolved NASH > placebo (25% v 3.9%)

Modified from: Singh S et al. Hepatology 2015.

Pentoxyfylline

- Moderate quality evidence to support ↓ steatosis, fibrosis, lobular inflammation
- Not mentioned in tri-society practice guidelines
- Safe medication
- GI side effects: nausea and/or vomiting
- Consider in patients not eligible for Vit E or Pioglitazone

Statins

- NASH pts often have ↑ lipids
- Statins=3-hydroxy-3-methyl-glutaryl coenzyme-A reductase (HMGCR inhibitors) → prevention of CV events & ↓ lipids
- ? Statin efficacy for treatment of NASH

[1] Van Rooyen DM et al. Gastroenterology 2011;141:1393-1403.

Statins

- Many NAFLD patients meet tx guidelines for statin therapy for CV benefit:
  - NAFLD pts also have ↑ LAEs, statins may further ↑ LAEs but RARELY cause serious liver disease
- **STATINS ARE SAFE TO USE IN NAFLD/NASH[1]**

[1]Chalasani N et al. Gastroenterology 2012;142:1592-1609.

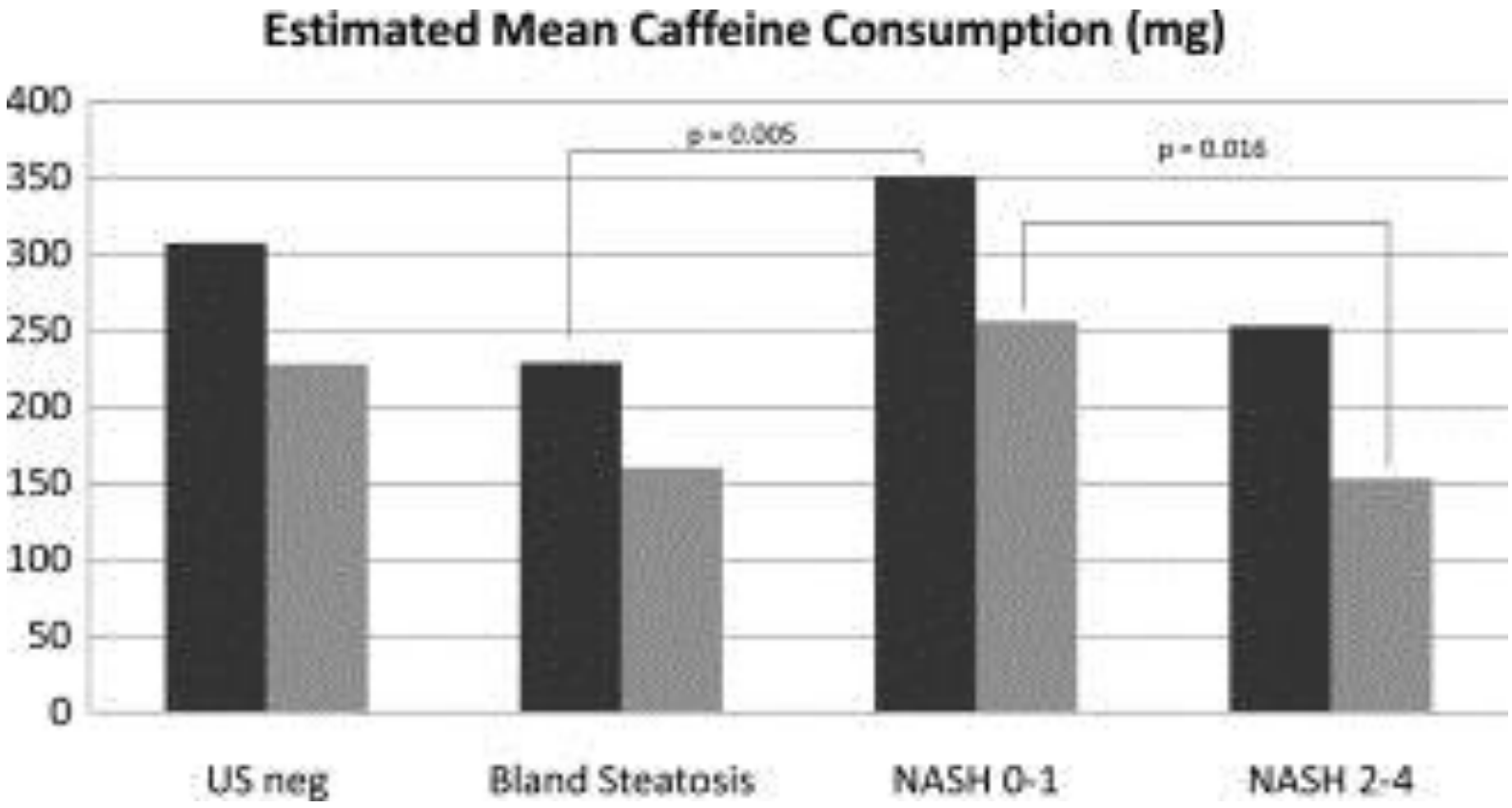
Statins

- Although safe, data on efficacy for NASH is limited, non-prospective, & usually without hepatic histology

Statins

- **Tri-society guidelines recommend statins for dyslipidemia in NASH patients but not specifically to treat NASH**
- **Use for hyperlipidemia in NASH, with some possible benefit for NASH although not confirmed**

Caffeinated Coffee & NAFLD



Molloy JW et al. Hepatology 2012.

Investigational therapies

- **Anti-fibrotic**
  - **Simtuzumab → Study terminated for lack of efficacy**
- **Anti-inflammatory**
  - **Elafibranor**
  - **Cenicriviroc**
  - **Galectin-3 antagonists**
  - **NOX-1 and NOX-4 inhibitors**
- **Hepato-protective**
  - **Farnesoid X nuclear receptor ligand**
  - **PPAR-α/δ agonist**
  - **Pan-caspase protease inhibitor**

Noureddin M et al. AP&T. June 2016

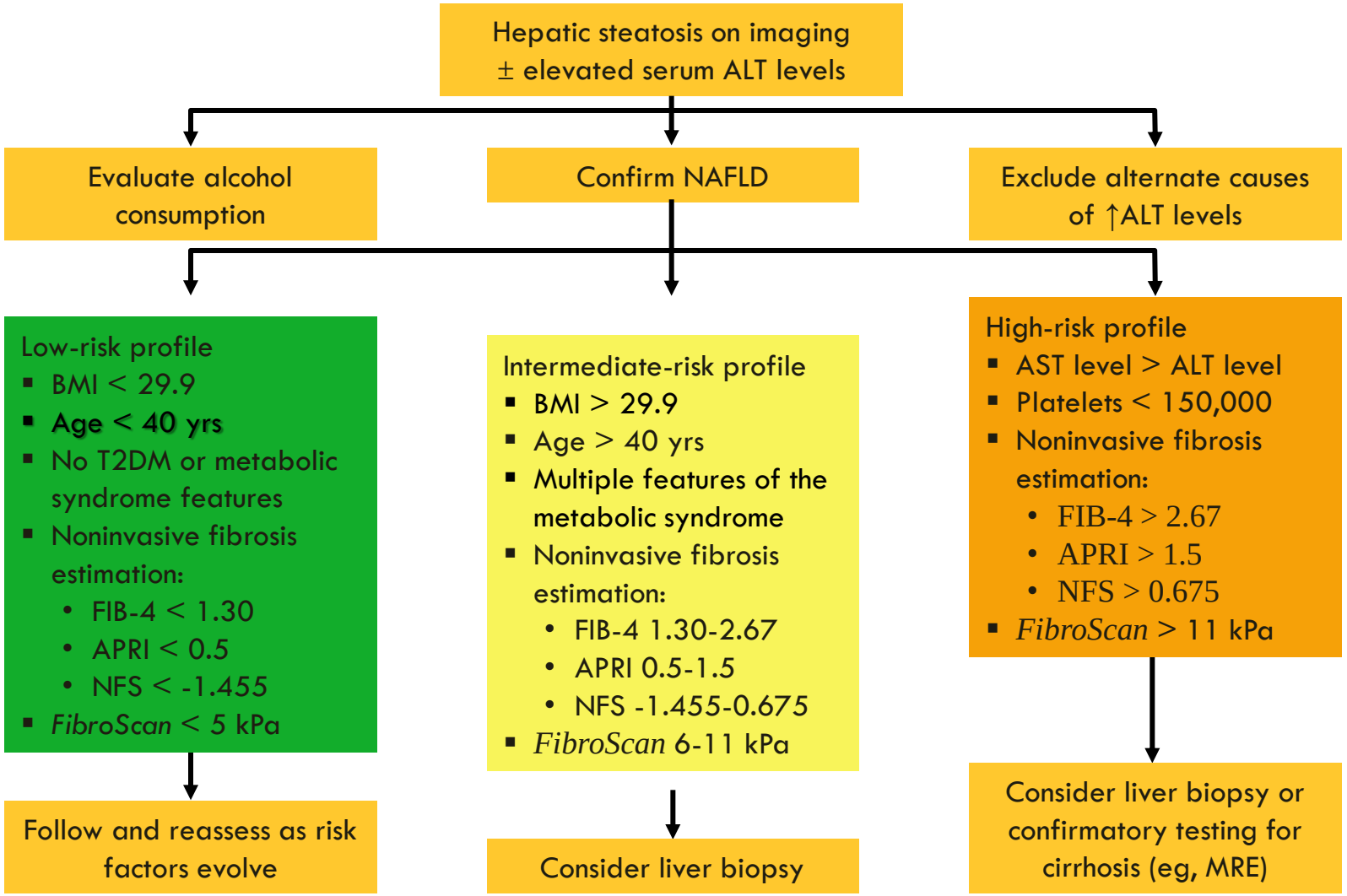
Obeticholic acid (OCA) (Farnesoid X nuclear receptor ligand)

	Obeticholic acid	Placebo	Relative risks or mean changes from baseline* (95% CI) (obeticholic acid *vs* placebo)	p value*
Primary outcome†				
Number of patients at risk‡	110	109		
Patients with improvement	50 (45%)	23 (21%)	2·2 (1·4 to 3·3)	0·0002
Changes from baseline in histological features				
Number of patients with biopsy specimens at baseline and 72 weeks	102	98		
Resolution§ of definite non-alcoholic steatohepatitis	22 (22%)	13 (13%)	1·7(0·9 to 3·2)	0·08
Fibrosis¶				
Patients with improvement	36 (35%)	19 (19%)	2·0 (1·2 to 3·4	0·004
Change in score	−0·2 (1·0)	0·1 (0·9)	−0·3 (−0·6 to −0·1)	0·01
Total NAFLD activity score				
Change in score	−1·7 (1·8)	−0·7 (1·8)	−0·9 (−1·3 to −0·5)	<0·0001
Hepatocellular ballooning				
Patients with improvement	47 (46%)	30 (31%)	1·5 (1·0 to 2·1)	0·03
Change in score	−0·5 (0·9)	−0·2 (0·9)	−0·2 (−0·5 to 0·0)	0·03
Steatosis				
Patients with improvement	62 (61%)	37 (38%)	1·6 (1·2 to 2·2)	0·001
Change in score	−0·8 (1·0)	−0·4 (0·8)	−0·4 (−0·6 to −0·2)	0·0004
Lobular inflammation				
Patients with improvement	54 (53%)	34 (35%)	1·6 (1·1 to 2·2)	0·006
Change in score	−0·5 (0·8)	−0·2 (0·9)	−0·3 (−0·5 to −0·1)	0·0006
Portal inflammation‖				
Patients with improvement	12 (12%)	13 (13%)	1·0 (0·5 to 2·2)	0·90
Change in score	0·2 (0·7)	0·2 (0·7)	0·0 (−0·1 to 0·2)	0·59

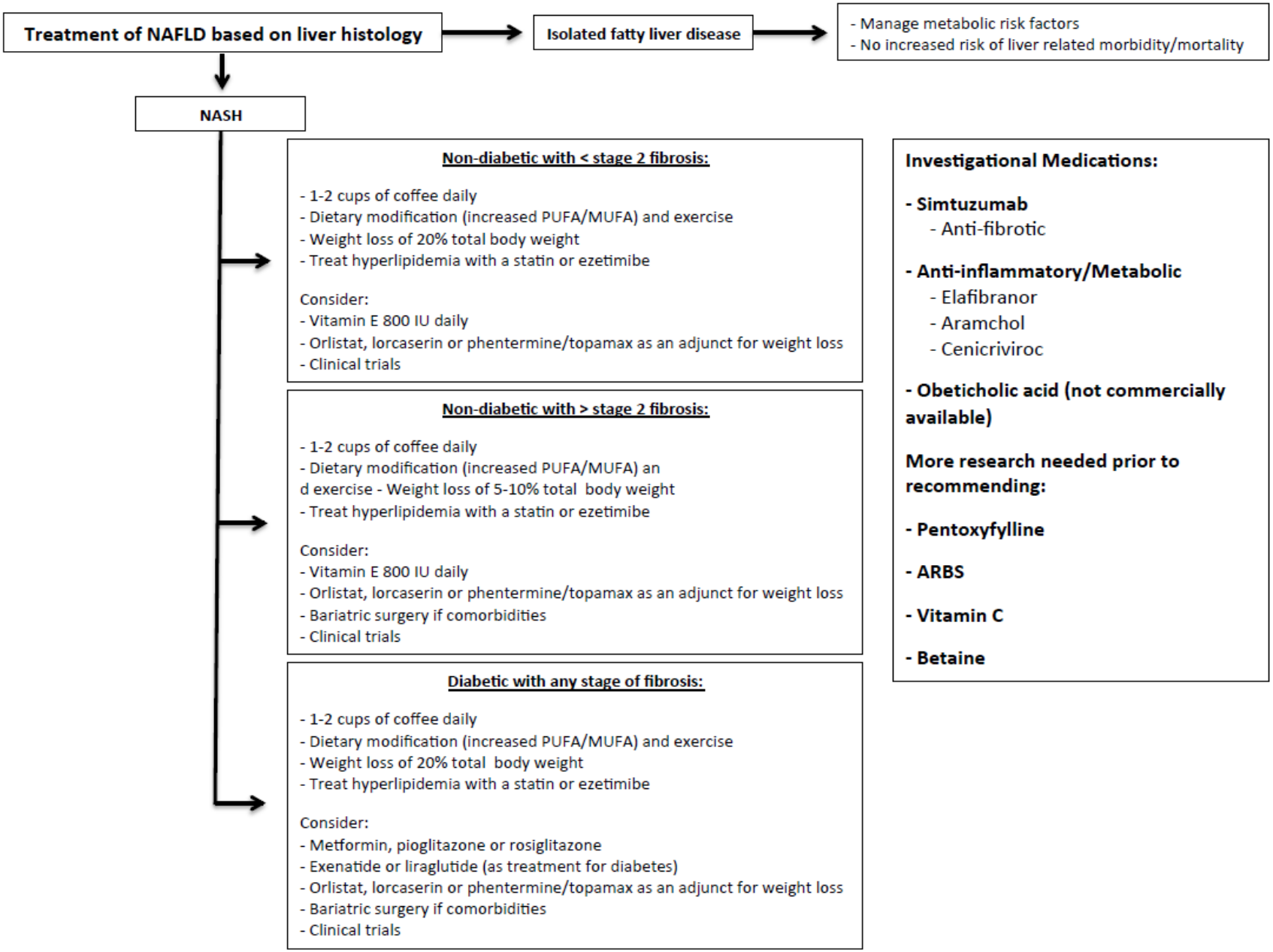
- **FLINT trial**
- **OCA improved NAS, ballooning, steatosis, lobular inflammation more than placebo**
- **Pruritus (33% versus 9% any itching)**
- **Lipid effects (↑ LDL)**

Neuschwander-Tetri B et al. FLINT Trial Lancet 2015: 385.

Risk Stratification in Pts With Suspected NAFLD



Rinella ME, Sanyal AJ. Nat Rev Gastroenterol Hepatol. 2016;13:196-205



Pence M, Stratton A, Torres DM et al. 2016 *in press.*

Therapies for NASH

Vitamin E 800–1000 IU daily	Improves NASH when used for 2 years. No fibrosis benefit.	Validation studies in diabetics and various ethnic groups needed to confirm benefit. May increase risk of prostate cancer.
Pioglitazone 30–45 mg daily	Improves NASH when used for 6 months to 2 years. May have a fibrosis benefit based on recent meta-analysis.	Expect a 4kg weight gain, possible increased risk for CHF and osteoporosis. Not FDA approved for NASH treatment. Limit use to those with stage 2 fibrosis or greater who failed an adequate challenge with diet and exercise.
Pentoxifylline	Improves NASH and fibrosis.	Small pilot trial data. Need confirmation in large, multi-centered trial.
Statins	Limited data on histopathology	Safe in NAFLD patients. Reduces risk of cardiovascular disease
Bariatric surgery		
RYGB, LAGB, sleeve gastrectomy	Improves or resolves NASH in 60–80% of cases. Likely fibrosis benefit as well	Lack of randomized, controlled trials. Caution in cirrhotic patients. Lifestyle modification attempted first.

Conclusions

- NAFLD most common cause of chronic liver disease
- NASH patients at risk of developing cirrhosis and have higher all cause mortality
- No FDA approved medications for NAFLD
  - Vitamin E 400 IU once daily
  - Actos 15-45 mg once daily for advanced disease
- Bariatric surgery can be effective
- **Lifestyle modification remains cornerstone of therapy**