Non-Alcoholic Fatty Liver Disease
An Update in Diagnosis, Management and Treatment Guidelines

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Definition

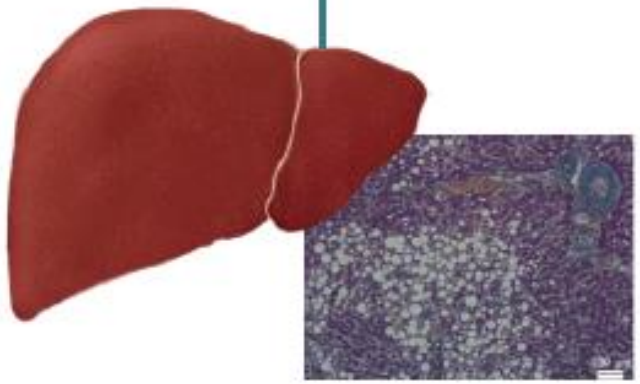
Defining Nonalcoholic Fatty Liver Disease

- Definition of NAFLD excludes significant alcohol use
- Significant alcohol use
  - >21 standard drinks on average per week in men
  - >14 standard drinks on average per week in women
  - Standard drink = ~14 grams of pure alcohol

Examples of "standard drinks"
12 ounces of 5% alcohol beer
8 ounces of 7% alcohol malt liquor
5 ounces of table wine
1.5 ounces of distilled spirits (40% alcohol)

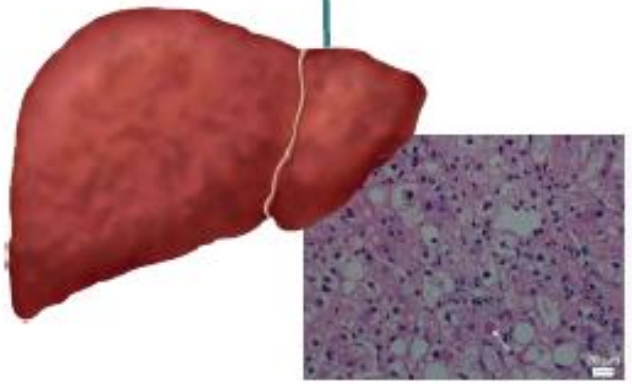
Chalasani N, et al. Hepatology 2018;67:328-357
Sanyal AJ, et al. Hepatology 2011;54:344-353

Depending on histologic criteria, NAFLD can be categorized into Nonalcoholic Fatty Liver (NAFL) or NASH



Steatosis (NAFL)

- Hepatic steatosis
- *No* evidence of hepatocellular injury (ballooning)
- *No* evidence of fibrosis



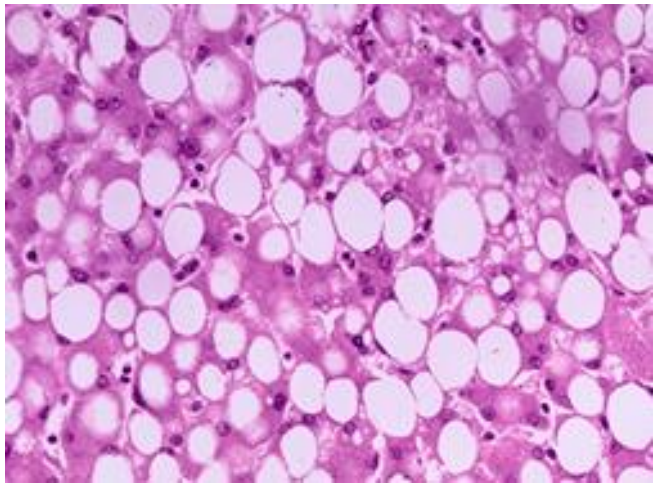
Steatohepatitis (NASH)

- Hepatic steatosis
- Inflammation
- Evidence of hepatocyte injury (ballooning)
- Presence or absence of fibrosis

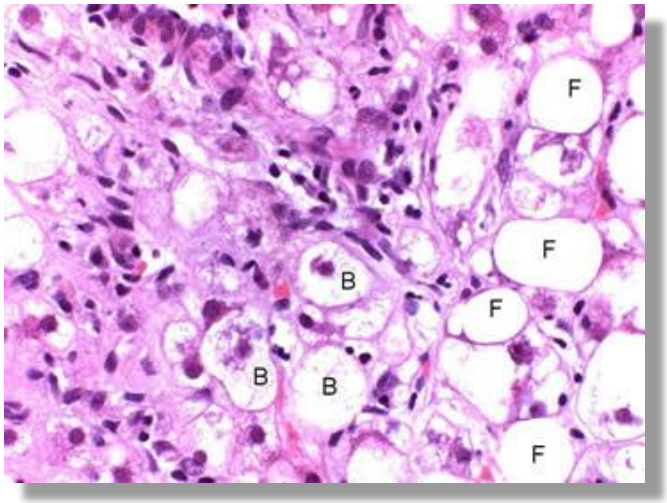
Note: Practice Guidance refers to simple steatosis as NAFL, thus the terms will be used interchangeably.

NAFL = nonalcoholic fatty liver; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

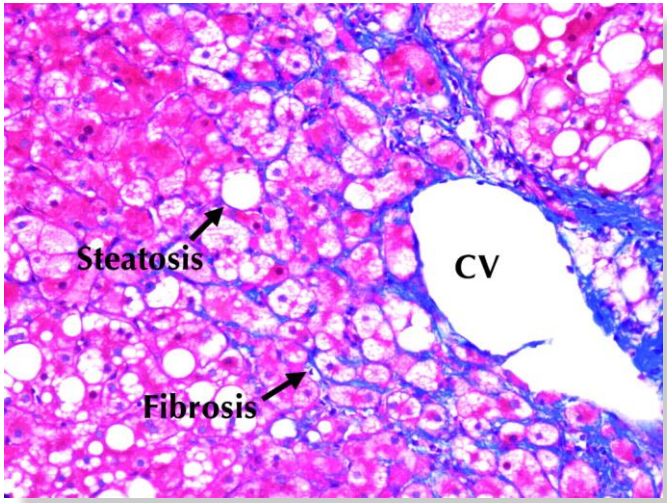
1. Chalasani N, et al. *Hepatology*. 2018;67(1):328–357.



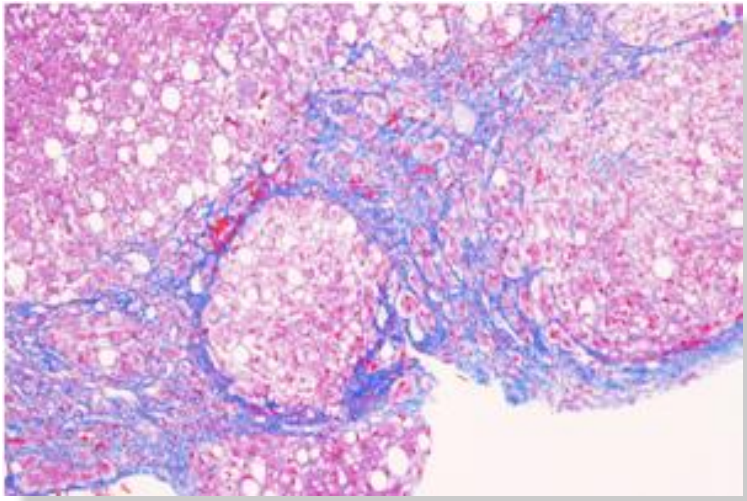
Fatty Liver



NASH – Fat + Ballooning + inflammation



Zone 3 pericellular and central vein fibrosis



Cirrhosis

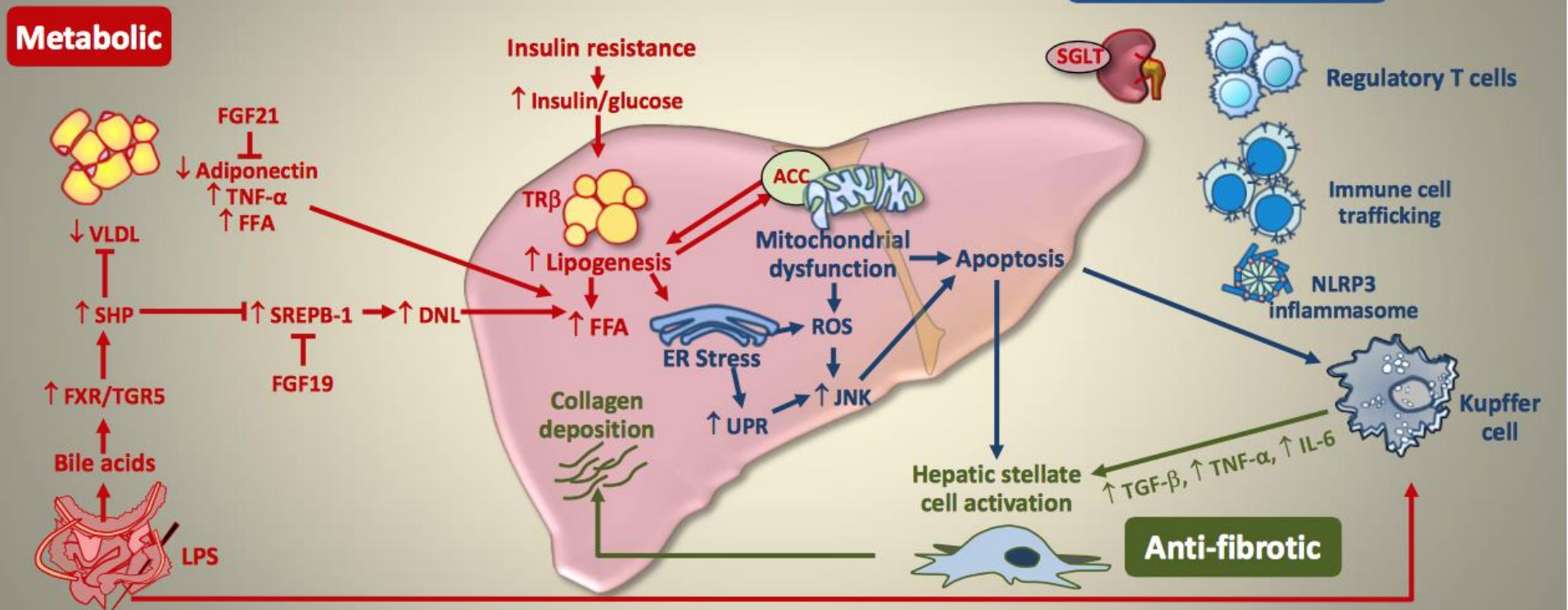
Pathogenesis of NAFLD

Pathogenesis of NAFLD

- **Excessive importation of FFA from adipose tissue**
  - Increased delivery of triglycerides to the liver (**obesity**)
  - Excessive conversion of carbohydrates and proteins to triglycerides (**overfeeding**)

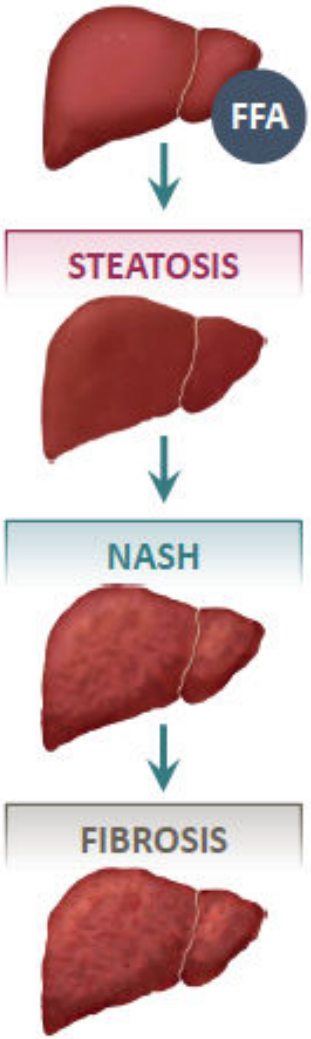
- **Diminished hepatic export of FFA (secondary to reduced synthesis or secretion of very low-density lipoprotein [VLDL])**

NASH: potential therapeutic targets



ACC, acetyl-CoA carboxylase; AOC, amine oxidase, copper containing; ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acids; FGF, fibroblast growth factor; FXR, farnesoid X receptor; IL, interleukin; JNK, Jun N-terminal kinases; LPS, lipopolysaccharide; NLRP3, nucleotide-binding oligomerization domain and leucine rich repeat and pyrin domain containing protein 3; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SCD, stearoyl CoA desaturase; SGLT, sodium-glucose linked transporter; SHP, small heterodimer partner; SREBP, sterol regulatory element binding proteins; TGF, transforming growth factor; TGR5, G protein-coupled bile acid receptor 1; TLR, toll like receptor; TNF, tumor necrosis factor; TR, thyroid receptor; UPR, unfolded protein response VLDL, very low density lipoprotein. Adapted from Konerman MA et al. *J Hepatol.* 2018;68:362–375.

Progression of Disease Activates an Inflammatory Cascade Contributing to Fibrogenesis[1-4]



- Metabolic syndrome
- Genetic factors
- Hepatocytes are less responsive to insulin

↓

- Increased fat storage
- Decreased fatty acid oxidation
- Fat droplets form in cells

↓

- Oxidative stress
- ER stress
- Mitochondrial dysfunction
- Lipotoxicity (apoptosis)
- Inflammation

↓

- Hepatic stellate cells lay down ECM deposits (fibrosis)

Image adapted from PIXOLOGICSTUDIO/SCIENCE PHOTO LIBRARY/Getty Images

ECM = extracellular matrix; ER = endoplasmic reticulum; FFA = free fatty acid; NASH = nonalcoholic steatohepatitis.

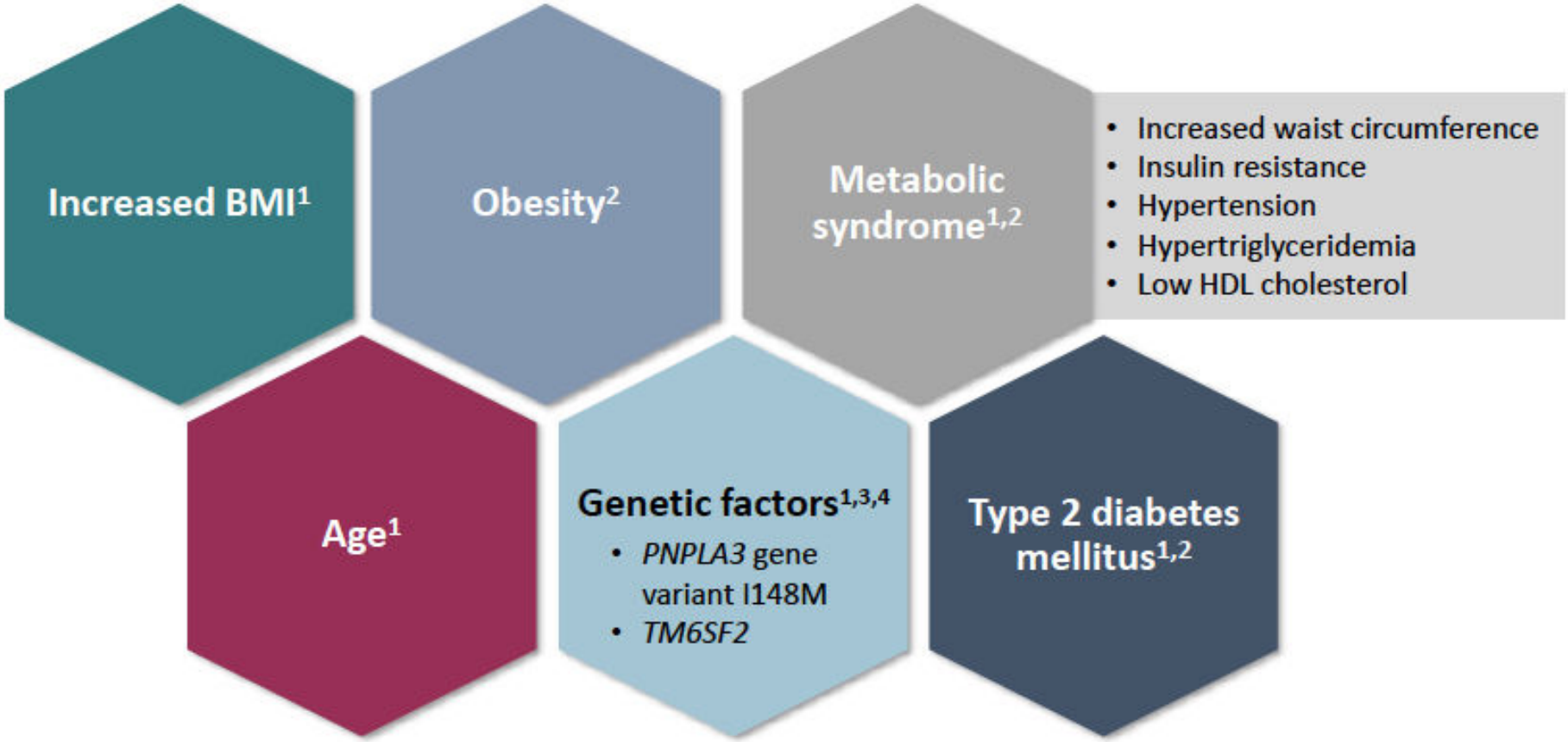
1. Schuppan D, et al. *J Gastroenterol Hepatol*. 2013;28(suppl 1):68–76; 2. Cusi K. *Gastroenterology*. 2012;142(4):711–725; 3. Machado MV, et al. *Gastroenterology*. 2016;150(8):1769–1777; 4. Ramos-Lopez O, et al. *World J Gastroenterol*. 2015; 21(41): 11552–11566.

Diagnosis of NAFLD

Suspect NAFLD

- Abnormal liver enzymes
- Radiological study of liver suggestive of fatty infiltration
- Search for risk factors

Risk Factors for Developing NASH and Disease Progression



BMI = body mass index; HDL = high-density lipoprotein; NASH = nonalcoholic steatohepatitis; *PNPLA3* = patatin-like phospholipase domain–containing protein 3; *TM6SF2* = transmembrane 6 superfamily member 2.

1. Marengo A, et al. *Clin Liver Dis.* 2016;20(2):313–324; 2. Chalasani N, et al. *Hepatology*. 2018;67(1):328–357; 3. Diehl AM, et al. *N Engl J Med.* 2017;377:2063–2072; 4. Anstee QM, et al. *Semin Liver Dis.* 2015;35:270–290.

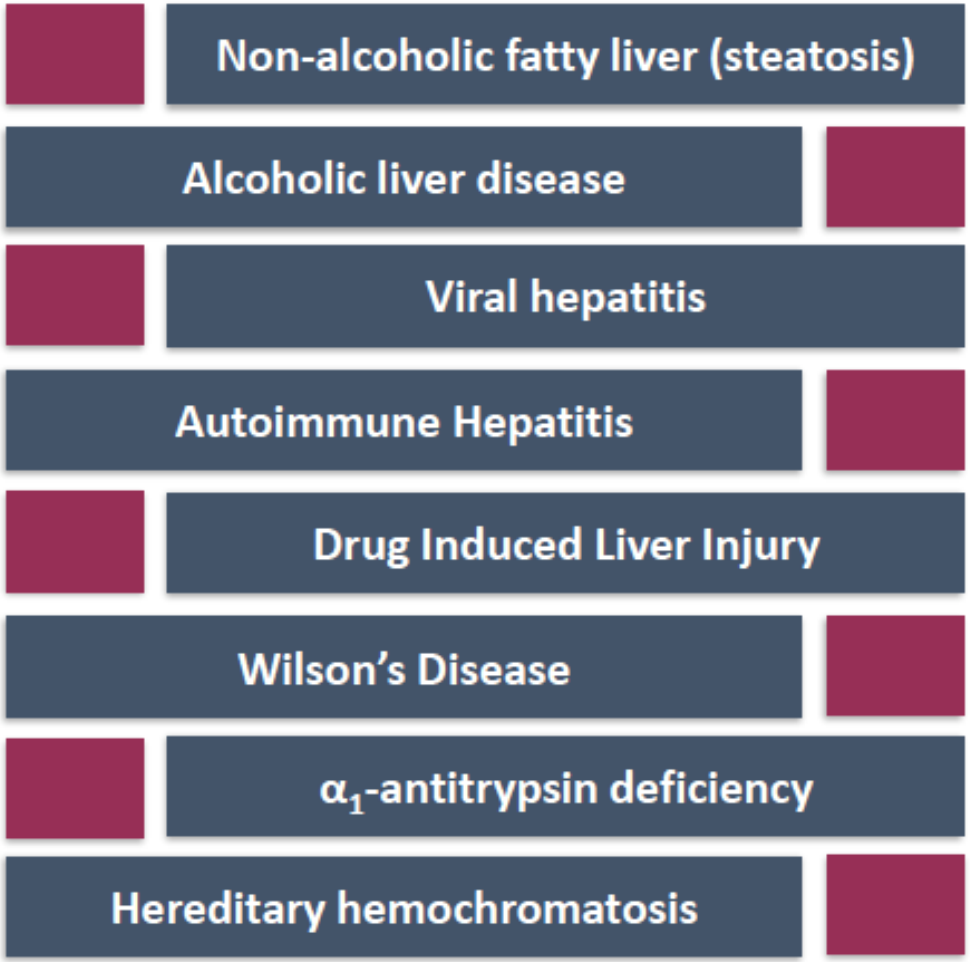
Assess for the Presence of the Metabolic Syndrome

- **Metabolic syndrome = 3 or more of the following:**

1. Waist circumference >102 cm in men or 88cm in women
2. Triglyceride level >150mg/dL
3. HDL cholesterol <40mg/dL in men, <50mg/dL in women
4. Systolic blood pressure >130mmHg or diastolic pressure >85 mmHg
5. Fasting plasma glucose level of >110mg/dl or diagnosis of diabetes

Grundy SM, et al. Circulation 2005;112:2735-2752

Select Other Diseases That May Result in Steatosis/Liver Disease



As part of assessing a patient suspected of NASH, other diseases should be ruled out[1,2,a]

[a]This list of other liver diseases to exclude is not exhaustive.

1. Chalasani N, et al. *Hepatology*. 2018;67:328-357; 2. Wilkins T, et al. *Am Fam Physician*. 2013;88(1):35-42.

Confusing Issues in the Laboratory Evaluation of NAFLD

- **Serum ferritin**
  - Often mildly elevated, does not reflect iron overload
  - If ferritin **and** transferrin saturation are elevated
    - Exclude genetic hemochromatosis
    - Consider liver biopsy to assess hepatic iron quantitation
- **Serum autoantibodies**
  - Frequently detected, often in low titers - epiphenomenon
  - Presence of antibodies does not impact natural history of NAFLD
  - Exclude autoimmune hepatitis if significant elevation of liver enzymes (>5x ULN) or elevated globulins

Valenti L, et al. Gastroenterology 2010;138:905-912
Vuppalanchi R, et al. Hepatol Int 2012;6:379-385

Diagnosis of NASH

- Liver Biopsy is the gold standard by which NASH diagnosis is established
- Limitations:
  - Risks involved
  - Painful
  - Costs
  - Sampling errors
  - Histologic interpretation

When to Obtain and Liver Biopsy in NAFLD – AASLD Guidance

- Patients at risk of having steatohepatitis and/or advanced fibrosis
  - Multiple features of the metabolic syndrome
  - NFS, FIB-4 or liver stiffness measurement suggesting advanced fibrosis
- Atypical presentation with need to exclude a competing etiology for NAFLD
- Evaluation for the presence or severity of co-existent chronic liver disease

Chalasani N, et al. Hepatology 2018;67:328-357

Screening for NAFLD in Primary Care and High Risk Groups – AASLD Guidance

1. General screening not cost-effective and not recommended
   - Gaps in natural history, diagnosis and treatment of NAFLD
2. Liver enzymes alone may be insensitive as screening tests
   - Elastography, fibrosis-4 index (FIB-4), and NAFLD fibrosis score (NFS) may be used in high risk patients
     - T2DM
3. Screening of family members not recommended

Chalasani N, et al. Hepatology 2018;67:328-357

NAFLD and Dietary Factors

Fatty Liver Risk Increases with Daily Intake of Sugary Drinks

- 5908 participants
- Adults who drink more than one sugar sweetened drink per day had 55% more chance of having Fatty Liver disease
- Sucrose and high fructose corn syrup

Journal of Hepatology 2015 vol 63; 462-469


Food Club
SINCE 1945
Tomato
Ketchup
NET WT 14 OZ (397g)


BEST WHEN USED BY 04000749300400
Nutrition Facts
Serv Size 1 Tbsp (16g)
Servings 32
Calories 10
Fat Cal 0
*Percent Daily Values (DV) are based on a 2,000 calorie diet.
Amount/serving %DV* Amount/serving %DV*
Total Fat 0g 0% Total Carb 2g 1%
Sodium 120mg 5% Sugars 1g
Protein 0g
Vitamin E 2% Vitamin K 0 %
Not a significant source of Sat Fat, Trans Fat, Cholest, Fiber, Vitamin A, Vitamin C, Calcium and Iron.
INGREDIENTS: WATER, MODIFIED FOOD STARCH, SUGAR, HIGH FRUCTOSE CORN SYRUP, VINEGAR, SOYBEAN OIL*, CONTAINS LESS THAN 2% OF SALT, CELLULOSE GEL, NATURAL FLAVOR, ARTIFICIAL COLOR, EGG YOLKS*, XANTHAN GUM, MUSTARD FLOUR, LACTIC ACID, CELLULOSE GUM, PHOSPHORIC ACID, VITAMIN E ACETATE, LEMON JUICE CONCENTRATE, DRIED GARLIC, DRIED ONIONS, SPICE, YELLOW 6, BETA CAROTENE, BLUE 1, WITH POTASSIUM SORBATE AND CALCIUM DISODIUM EDTA AS PRESERVATIVES.
*TRIVIAL SOURCE OF FAT AND CHOLESTEROL
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0 21000 64005 8
FAT FREE MAYO 16 OZ


Salad Lover
Check the Back!
Wish-Bone
Deluxe French
Dressing
8 FL OZ (237 mL)

Nutrition Facts

Serv. Size 2 tbsp (30mL)
Servings 8
Calories 120
Fat Cal. 100

*Percent Daily Values (DV) are based on a 2,000 calorie diet.

Amount/serving	% DV*	Amount/serving	% DV*
Total Fat 11g	**17%**	**Potassium** 15mg	**0%**
Sat. Fat 1.5g	**8%**	**Total Carb.** 5g	**2%**
Trans Fat 0g		Dietary Fiber 0g	**0%**
Cholest. 0mg	**0%**	Sugars 5g	
Sodium 170mg	**7%**	**Protein** 0g	

Vitamin A 4% • Vitamin C 0% • Calcium 0% • Iron 0%

INGRE HIGH FRUCTOSE CORN SYRUP, VINEGAR (CIDER, CORN SUGAR DISTILLED), TOMATO PASTE, SALT, SPICE, ONION POWDER, XANTHAN GUM, PROPYLENE GLYCOL ALGINATE, PAPRIKA OLEORESIN, NATURAL FLAVORS, CALCIUM DISODIUM EDTA (USED TO PROTECT QUALITY).

Questions or comments?
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0 41000 00652 4

DELUXE FRENCH
83018513


Per Serving
CALORIES
110
FAT
FREE
0g
VITAMINS
& MINERALS
Kellogg's
Special
KD
lightly toasted rice cereal

INGREDIENTS: RICE, WHOLE GRAIN WHEAT, SUGAR, BERRY OAT CLUSTERS (TOASTED OATS [ROLLED OATS, SUGAR, SOYBEAN OIL, HONEY, BROWN SUGAR, MOLASSES], SUGAR, ROLLED OATS, FLAVORED APPLES [APPLES, ARTIFICIAL FLAVOR, CITRIC ACID, RED #40 LAKE, SODIUM SULFITE TO PRESERVE COLOR], CORN SYRUP, BROWN SUGAR, NATURAL AND ARTIFICIAL FLAVOR, BHT FOR FRESHNESS), VANILLA FLAVORED CLUSTERS (SUGAR, TOASTED OATS [ROLLED OATS], CORN SYRUP, HIGH FRUCTOSE CORN SYRUP, PARTIALLY HYDROGENATED SOYBEAN OIL, MOLASSES, HONEY], ROLLED WHEAT, CRISP RICE [RICE, SUGAR, MALT, SALT], CORN SYRUP, HONEY, CINNAMON, ARTIFICIAL FLAVOR, BHT FOR FRESHNESS), HIGH FRUCTOSE CORN SYRUP, SALT, FRACTIONATED PALM KERNEL OIL, MALT FLAVOR, NONFAT DRY MILK, NONFAT YOGURT POWDER (CULTURED NONFAT MILK, YOGURT IS HEAT TREATED AFTER CULTURING), WHEY, ASCORBIC ACID (VITAMIN C), CONFECTIONER'S GLAZE, NATURAL AND ARTIFICIAL FLAVORS, CORN SYRUP SOLIDS, PARTIALLY HYDROGENATED PALM OIL, REDUCED IRON, NIACINAMIDE, TAPIOCA DEXTRIN, SOY LECITHIN, MALTODEXTRIN, PYRIDOXINE HYDROCHLORIDE (VITAMIN B_6), RIBOFLAVIN (VITAMIN B_2), THIAMIN HYDROCHLORIDE (VITAMIN B_1), VITAMIN A PALMITATE, BHT FOR FRESHNESS, FOLIC ACID, VITAMIN B_{12}, VITAMIN D.

CONTAINS WHEAT, MILK AND SOY INGREDIENTS.

Exchange: 1 1/2 Carbohydrates

The dietary exchanges are based on the *Exchange Lists for Meal Planning*, ©2003 by The American Diabetes Association, Inc. and The American Dietetic Association.


KRAFT
MAYO
FAT FREE
MAYONNAISE DRESSING
ZERO grams of fat
Did You Know
CARB COUNT
2g
COUNT CALORIES TOO
Pareve

BEST WHEN USED BY 04000749300400

Nutrition Facts

Serv Size 1 Tbsp (16g)
Servings 32
Calories 10
Fat Cal 0
*Percent Daily Values (DV) are based on a 2,000 calorie diet.

Amount/serving	%DV*	Amount/serving	%DV*
Total Fat 0g	0%	**Total Carb** 2g	1%
Sodium 120mg	5%	Sugars 1g	
		Protein 0g	
Vitamin E 2%		Vitamin K 0 %	

Not a significant source of Sat Fat, Trans Fat, Cholest, Fiber, Vitamin A, Vitamin C, Calcium and Iron.

INGREDIENTS: WATER, MODIFIED FOOD STARCH, SUGAR, HIGH FRUCTOSE CORN SYRUP, VINEGAR, SOYBEAN OIL*, CONTAINS LESS THAN 2% OF SALT, CELLULOSE GEL, NATURAL FLAVOR, ARTIFICIAL COLOR, EGG YOLKS*, XANTHAN GUM, MUSTARD FLOUR, LACTIC ACID, CELLULOSE GUM, PHOSPHORIC ACID, VITAMIN E ACETATE, LEMON JUICE CONCENTRATE, DRIED GARLIC, DRIED ONIONS, SPICE, YELLOW 6, BETA CAROTENE, BLUE 1, WITH POTASSIUM SORBATE AND CALCIUM DISODIUM EDTA AS PRESERVATIVES.
*TRIVIAL SOURCE OF FAT AND CHOLESTEROL

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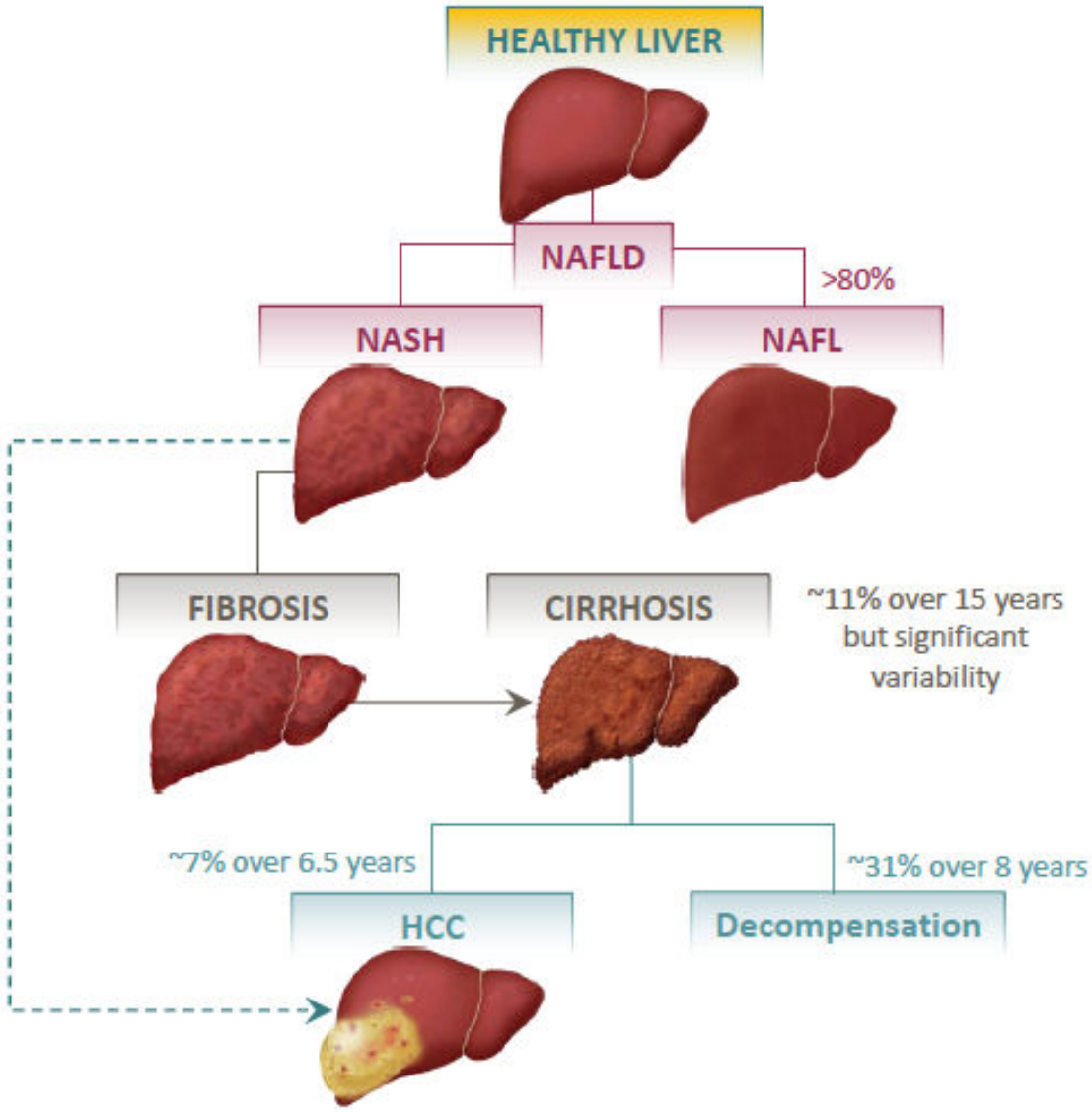
FAT FREE MAYO 16 OZ

Fibrosis: Predictor of Disease Progression and of Negative Outcomes

Natural History of NASH



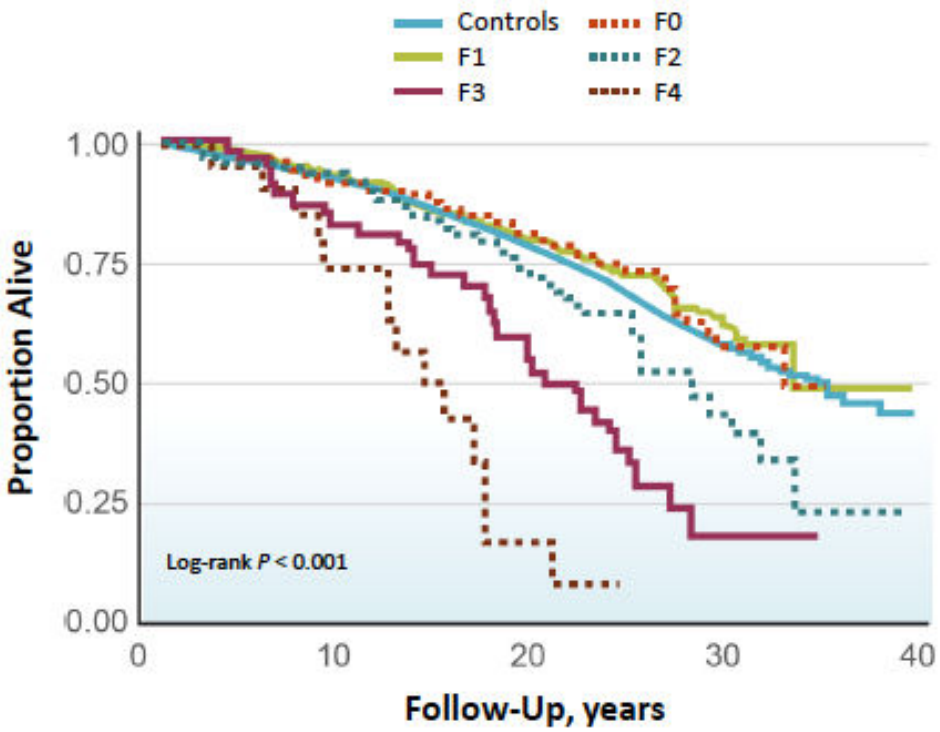
Patients with NASH are at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma.

HCC = hepatocellular carcinoma; NAFL = nonalcoholic fatty liver; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

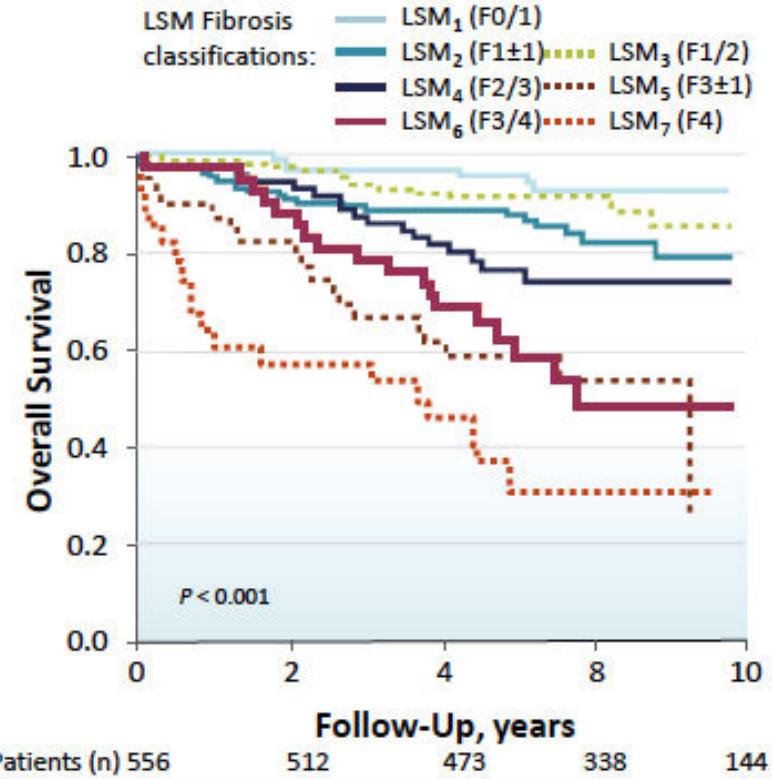
1. Torres DM, et al. *Clin Gastroenterol Hepatol*. 2012;10(8):837–858.

Fibrosis Is the Most Robust Predictor of Mortality and the Development of End-Stage Liver Disease

Overall Mortality Stratified by Fibrosis Stage Scored by Kleiner Classification (Swedish Retrospective Cohort in Patients With Biopsy-Proven NAFLD, n=646)[1]



Overall Mortality Stratified by Fibrosis Stage Classified by FibroScan (French Longitudinal Cohort in Patients With Biopsy-Proven NAFLD, n=556)[2]



Two distinct cohorts depicted by Kleiner classification and FibroScan indicate that overall mortality can be predicted by liver fibrosis

LSM, liver stiffness measurement.

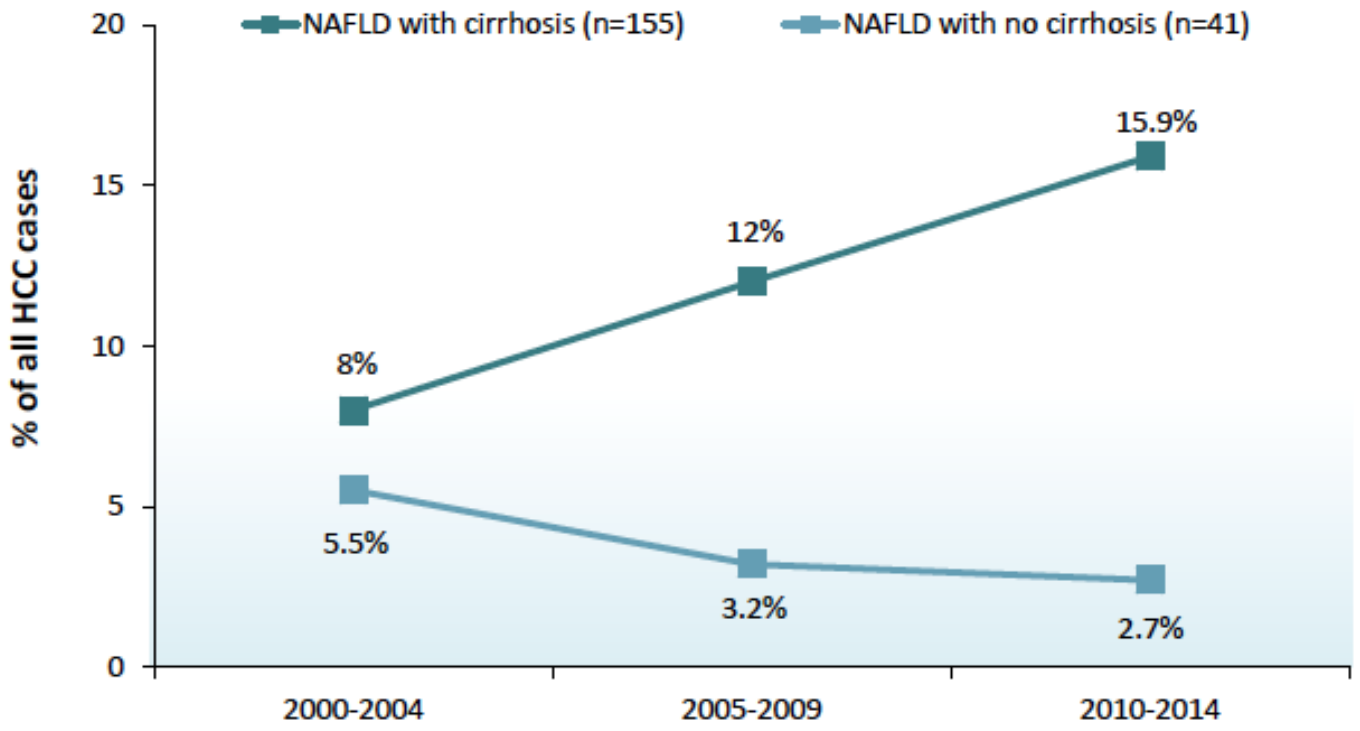
Left figure: reprinted from *J Hepatol*, 67(6), Hagström H, et al. 1265–1273, © 2017, with permission from Elsevier.

Right figure reprinted from *J Hepatol*, 65(3), Boursier J, et al. 570–578, © 2016, with permission from Elsevier.

1. Hagström H, et al. *J Hepatol.* 2017;67(6):1265–1273; 2. Boursier J, et al. *J Hepatol.* 2016;65(3):570–578.

Increasing Frequency of HCC in Patients With NAFLD Is Primarily Driven by Those With Cirrhosis

Trends in Cirrhotic and Noncirrhotic NAFLD-linked HCC Cases Over Time in a Cancer Registry in the US (N=196)[1]



In patients with NASH, HCC can also occur in the absence of cirrhosis[2]

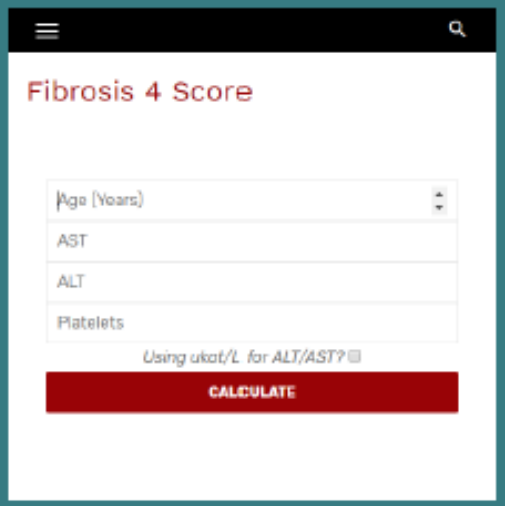
HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease; US = United States.

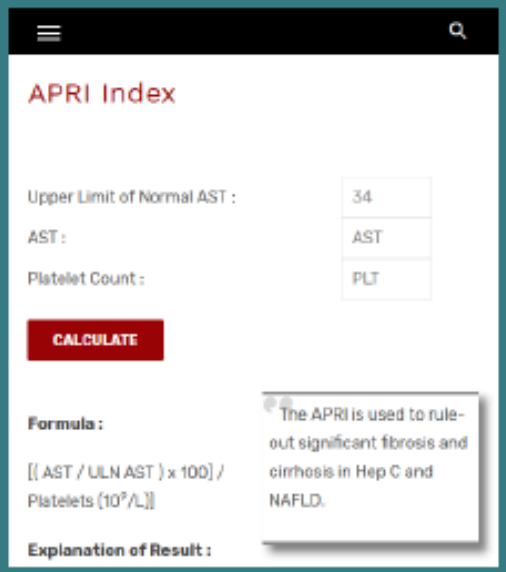
1. Dakhoul L, et al. Presented at: The Liver Meeting; Washington, DC; October 20-24, 2017; Abstract 2119(poster presentation); 2. Kawada N, et al. *J Gastroenterol*. 2009;44(12):1190–1194.

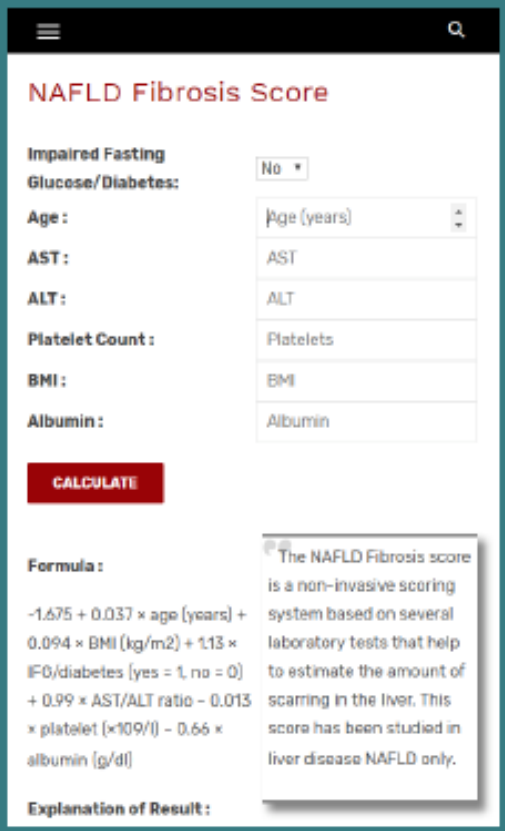
Noninvasive Diagnosis of Fibrosis in Adults with NAFLD

- Serologic markers
  - Simple:
    - **FIB-4**
    - **NFS**
    - **APRI index**
  - Complex:
    - **FibroSpect**
    - **ELF (Enhanced Liver Fibrosis)**
    - **Pro-C3**
    - **FibroTest or FibroSure**

Scores for Simple Noninvasive Biomarker Tests Can Be Easily Calculated







Online tools can be used for the calculation of APRI, FIB-4, and NFS scores, which are based on routinely available patient data[1,2]

1. Chalasani N, et al. *Hepatol*. 2018;67:328-357. 2. http://gihep.com/calculators/hepatology/

Noninvasive Diagnosis of Fibrosis in Adults with NALFD: Complex Serologic Markers

- **FibroSpect**
  - Alpha-2 macroglobulin
  - Hyaluronic acid
  - Tissue inhibitor of metalloproteinase 1 (TIMP-1)
- **ELF Panel**:
  - Procollagen III amino terminal peptide (PIIINP)
  - Hyaluronic acid
  - Tissue inhibitor of metalloproteinase 1 (TIMP-1)
- **PRO-C3**
  - Marker of type III collagen formation

Noninvasive Diagnosis of Fibrosis in Adults with NALFD: Complex Serologic Markers

- **FibroTest or FibroSure**
  - Age
  - Gender
  - Alpha-2-macroglobulin
  - Haptogobin
  - Apolipoprotein A1
  - Gamma-glutamyl transpeptidase
  - ALT

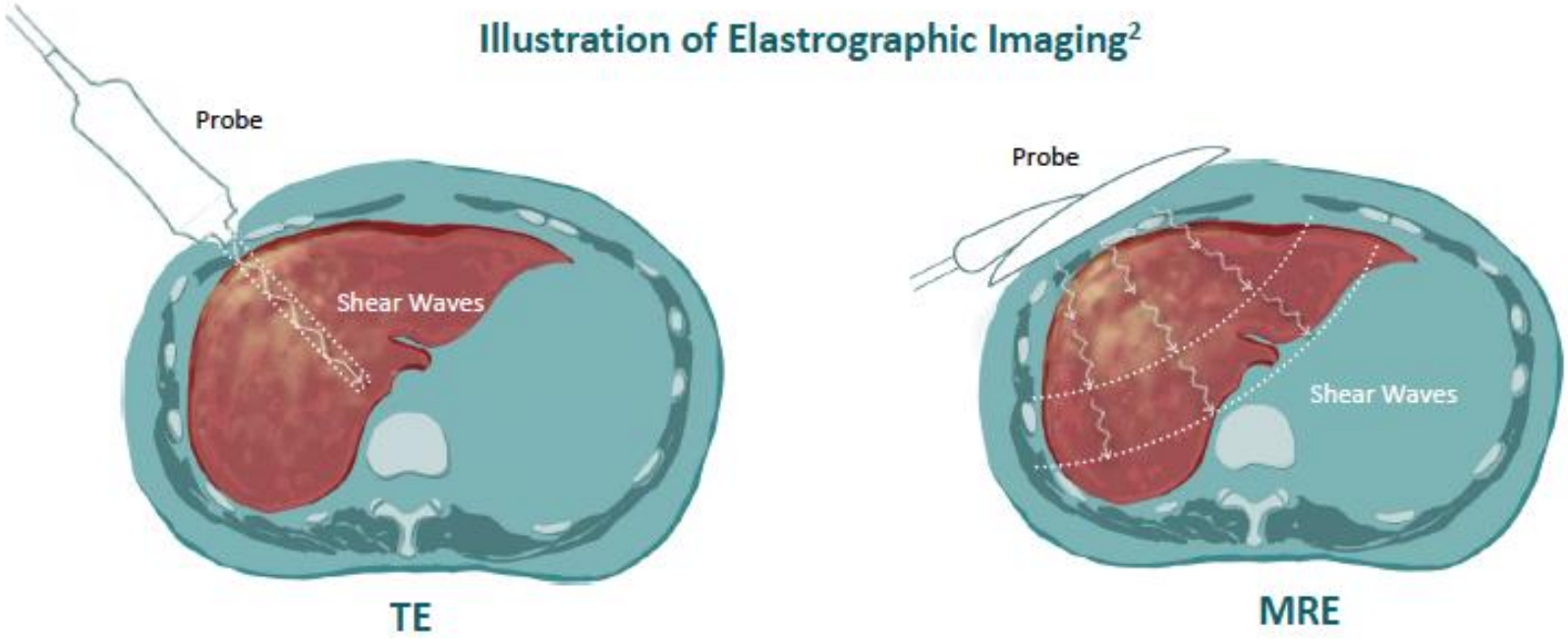
Noninvasive Diagnosis of Fibrosis in Adults with NAFLD

- Imaging
  - VCTE or Fibroscan
  - MRE

Elastography May Offer a Reliable Method for Detecting Advanced Fibrosis due to NASH

- Liver stiffness steadily increases with increasing severity of liver fibrosis[1]
- Noninvasive imaging techniques can be used to assess liver stiffness (measured in kPa), which correlates with fibrosis[2]
- Two clinically useful noninvasive imaging tools for detecting advanced fibrosis are[3]:
  1. Transient elastography (TE)
  2. Magnetic resonance elastography (MRE)

Illustration of Elastrographic Imaging[2]



1. Venkatesh SK, et al. *J Magn Reson Imaging*. 2013;37(3):544-555. 2. Mikolasevic I et al. *World J Gastroenterol* 2016;22(32):7236–7251; 3. Chalasani N, et al. *Hepatol*. 2018;67:328-357.

AASLD Guidance

1. In patients with NAFLD, MetS predicts the presence of steatohepatitis and can be used to target patients for liver biopsy
2. NFS or FIB-4 index are clinically useful tools for identify NAFLD patients with higher likelihood of having stage 3 or 4 fibrosis
3. VCTE or MRE are clinically useful tools for identifying advanced fibrosis in patients with NAFLD

Chalasani N, et al. Hepatology 2018;67:328-357

Management of NAFLD

Who to Treat

Goals of Treatment:

- Management of metabolic comorbidities
- Pharmacologic treatments aimed at improving liver disease
  - Patients with biopsy proven NASH and fibrosis

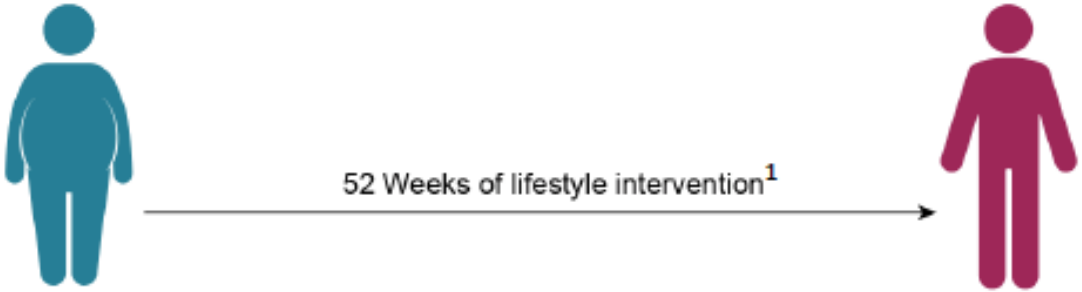
Chalasani N, et al. Hepatology 2018;67:328-357

Treatment

- Weight loss
- Lifestyle interventions
- Insulin Sensitizers: Metformin and Pioglitazone
- Vitamin E
- GLP 1 agonists
- Ursodeoxycholic acid and Omega 3 fatty acids
- Bariatric surgery
- Novel Medications

Increasing Benefit of Weight Loss Seen With NASH Resolution and Fibrosis but With Significant Variability in Response

Increased likelihood of NASH resolution and fibrosis improvements was associated with higher degrees of weight loss[1]



Weight loss, %	5%	7%	10%	P-value
Resolution of steatohepatitis,[a] %	10%	26%	64%	90%	<0.01
Fibrosis regression,[b] %	16%	18%	16%	45%	<0.01
Steatosis improvement,[c] %	35%	65%	76%	100%	<0.001
Patients achieving weight loss, %	70%	12%	9%	10%	
N =293	n=205	n=34	n=25	n=29	

In this study, only

1 in 5 patients may achieve weight loss sufficient (≥7%) to significantly improve liver histology[1]

The presence of diabetes, BMI ≥35, female sex, and many ballooned cells at baseline reduced the probability of NAS improvement or resolution of steatohepatitis[1]

Weight loss through lifestyle interventions can be difficult to sustain[2,3]

[a]Resolution of steatohepatitis was defined as absence of the histologic features of definite steatohepatitis, which required lack of hepatocellular ballooning with no fibrosis impairment. [b]Regression was defined as a decrease of at least 1 point in the fibrosis score. [c]Improvement in steatosis, ballooning, lobular formation, and portal inflammation scores were defined as a reduction of at least 1 point as compared with baseline values with no fibrosis impairment.

1. Vilar-Gomez E, et al. *Gastroenterology*. 2015;149(2):367-378; 2. Managing Overweight and Obesity in Adults: Systematic Evidence Review from the Obesity Expert Panel. National Institutes of Health; 2013. https://www.nhlbi.nih.gov/health-topics/managing-overweight-obesity-in-adults. Accessed September 2019; 3. Anderson JW et al. Am J Clin Nutr 2001;74:579–584.

Lifestyle Intervention

- Lifestyle Intervention – Exercise
- Exercise improves hepatic steatosis
- Optimal exercise regimen
  - Maintain physical activity 150 min/week
  - Exercise > 5x week
- Best outcomes if exercise is combined with weight loss

Keating SE, Hackett DA, Parker HM, et al. J Hepatol 2015;63:174-182
Houghton D, Thoma C, Hallsworth K, et al. Clin Gastroenterol Hepatol 2017;15:96-102

Recommended Dietary Modifications

- Mediterranean diet
- Ingestion of food without labels
- 60 ml of extra virgin olive oil
- Nuts
- Avoidance of high fat foods: animal fat and red meat

Insulin Sensitizers - Metformin

- Improves insulin resistance
- May improve serum aminotransferases
- No significant improvement in liver histology

Marchesini G, et al. Lancet 2001;358:893-894
Nair S, et al. Aliment Pharmacol Ther 2004;20:23-28
Bugianesi E, et al. Am J Gastroenterol 2005;100:1082-1090

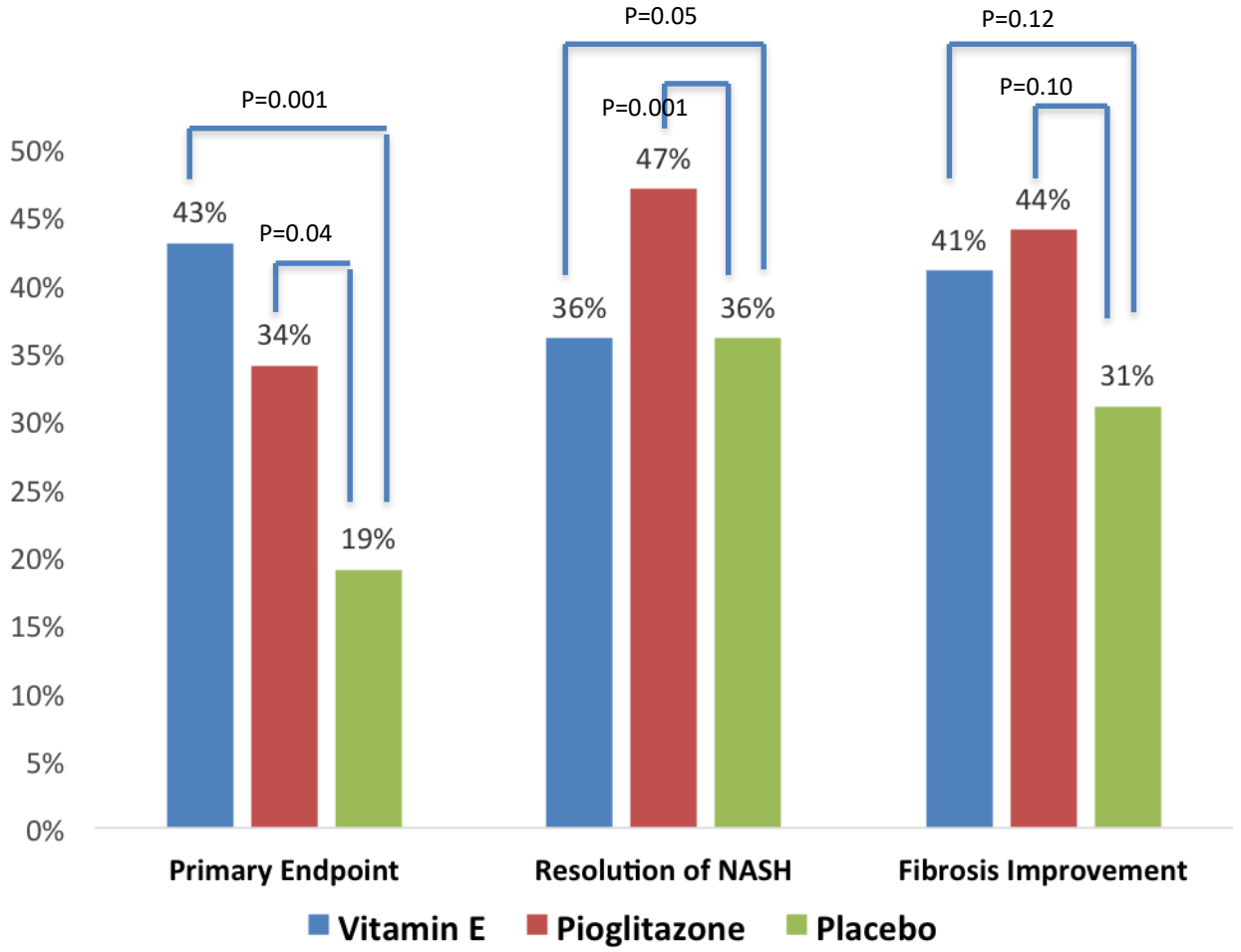
Antioxidants - Vitamin E

- PIVENS trial, non-diabetic patients
  - 247 patients randomized for 24 months to
    - Pioglitazone 30 mg/day
    - Vitamin E 800 IU/day (*rrr α-tocopherol)*
    - Placebo
  - Primary Endpoint
    - Improvement in histology by $\geq$2 points (including at least 1 point in ballooning and 1 point in inflammation or steatosis) + no increase in fibrosis

Sanyal AJ, et al. NEJM 2010;362:1675-85

Insulin Sensitizers – Pioglitazone

- PIVENS trial results
  - Due to study design significant p value <0.025



Sanyal AJ, et al. NEJM 2010;362:1675-85

Pioglitazone - Concerns

- Weight gain
  - Improved insulin action
  - Increased adipose tissue triglyceride synthesis
  - 2.5 to 4.7 kg over 12 to 36 months
- Bladder cancer
  - Population-based studies yield conflicting results
  - Cohort of 193,099 persons aged >40 followed for over 16 years – no association with bladder cancer
- Bone loss
  - Higher risk: women treated with pioglitazone

Tuccori M, et al. BMJ 2016;352:i1541
Lewis JD, et al JAMA 2015;314:265-277
Yau H, et al. Curr Diab Rep 2013;13:3290-341

Pioglitazone – AASLD Guidance

1. In biopsy proven NASH, pioglitazone improves histology in patients with and without diabetes
2. Risks and benefits should be discussed with each patient
3. Should not be used to treat NAFLD without biopsy proven NASH

Chalasani N, et al. Hepatology 2018;67:328-357

Vitamin E

- Improves oxidative stress, a key mechanism of hepatocellular injury in NASH
- Studies of vitamin E difficult to analyze
  - Varying criteria for enrollment
  - Unclear formulation of vitamin E used
    - Pure form of *rrr* α-tocopherol may be best absorbed

Chalasani N, et al. Hepatology 2018;67:328-357

Vitamin E

- Summary of studies in NASH
  - Vitamin E decreases serum aminotransferases
  - Improves steatosis, inflammation and ballooning and achieves resolution of NASH in a subset of nondiabetic patients
  - No effect on hepatic fibrosis

Chalasani N, et al. Hepatology 2018;67:328-357

Vitamin E - Concerns

- Questionable association with long-term all-cause mortality with doses >800IU/d
- One study found an association with increased risk of prostate cancer

Abner EL, et al. Curr Aging Sci 2011;4:158-170
Klein EA, et al. JAMA 2011;306:1549-1556

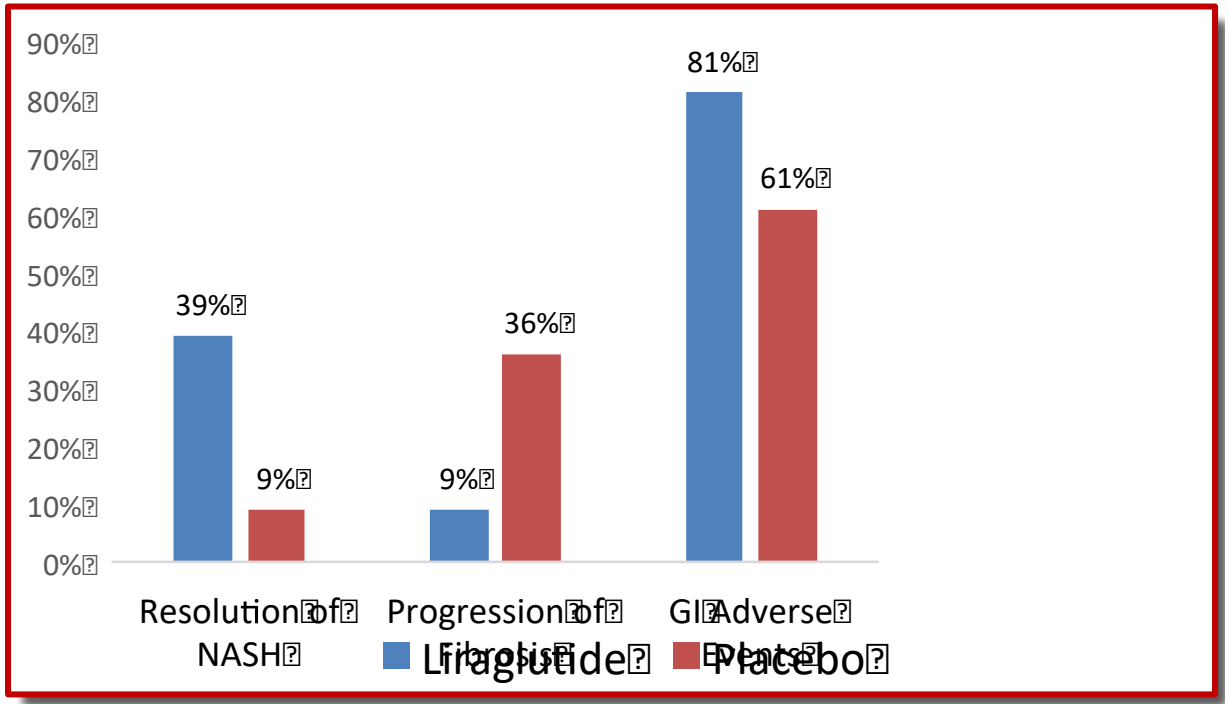
Vitamin E – AASLD Guidance

1. Vitamin E (*rrr* α-tocopherol) 800 IU/day improves liver histology in nondiabetic with biopsy proven NASH
2. Risk and benefits should be discussed with each patient
3. Vitamin E is not recommended to treat NAFLD without biopsy proven NASH

Chalasani N, et al. Hepatology 2018;67:328-357

Glucagon-Like Peptide-1 Analogues (GLP-1)

- Associated with weight loss
- Stimulates glucose-dependent insulin release
- 52 patients, biopsy proven NASH
- Randomized to
  - Liraglutide subcutaneously once a day x 48 weeks
  - Placebo injections



Armstrong MJ, et al. Lancet 2016;387:679-90

GLP-1 Agonists – AASLD Guidance Statement

1. It is premature to consider GLP-1 agonists to treat NAFLD with NASH

Chalasani N, et al. Hepatology 2018;67:328-357

Ursodeoxycholic Acid and Omega-3 Fatty Acids – AASLD Guidance

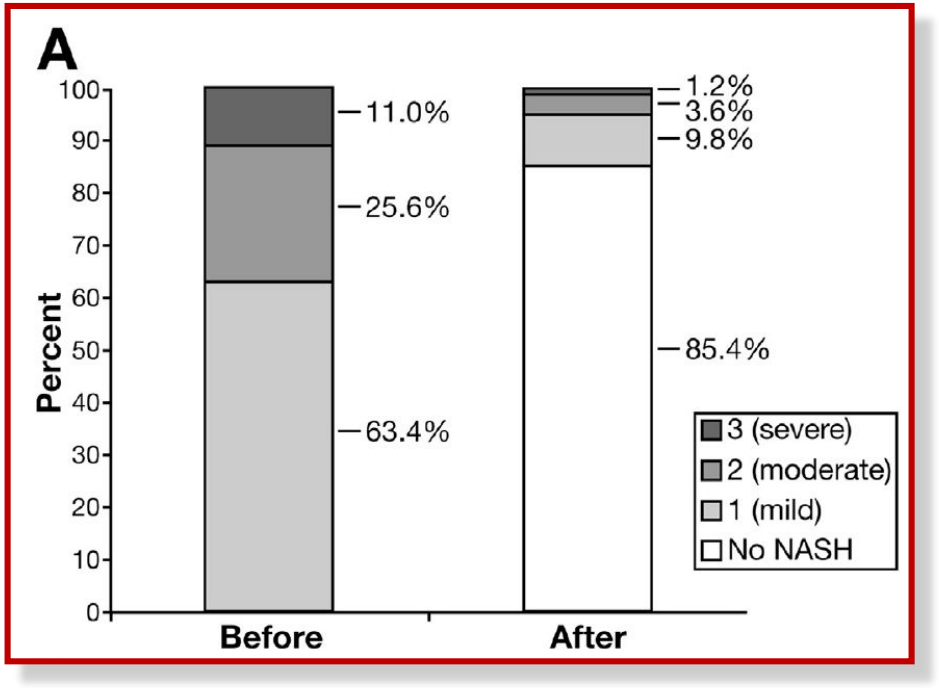
1. Ursodeoxycholic acid is not recommended for the treatment of NAFLD or NASH

2. Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but may be used to treat hypertriglyceridemia in patients with NAFLD

Chalasani N, et al. Hepatology 2018;67:328-357

Bariatric Surgery

- Prospective analysis of 109 patients with NASH at time of bariatric surgery
  - Liver biopsy repeated 1 year post surgery
  - 85% had NASH resolution
  - Fibrosis improved in 33%



NASH Grade Before and 1 Year Post Surgery

Lassailly G, et al,. Gastroenterology 2015;149:379-388

Bariatric Surgery - Safety

- Safety and efficacy of bariatric surgery in NASH not well established
- Higher mortality in cirrhosis
  - No cirrhosis (0.3% mortality)
  - Compensated cirrhosis (0.9%)
  - Decompensated cirrhosis (16.3%)
  - Sleeve gastrectomy may be safer

Chalasani N, et al. Hepatology 2018;67:328-357
Mosko JD, et al. Clin Gastroenterol Hepatol 2011;9:897-901
Jan A, et al. Obes Surg 2015;25:1518-1526

Bariatric Surgery – AASLD Guidance

1. Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH
2. Bariatric surgery is not yet an established option to specifically treat NASH
3. Type, safety and efficacy of bariatric surgery in otherwise eligible patients with cirrhosis is not established

Chalasani N, et al. Hepatology 2018;67:328-357

Management of Cardiovascular Disease and Dyslipidemia

- Strong association between NAFLD and increased risk of cardiovascular disease
- In patients with elevated liver tests and dyslipidemia, statins
  - Reduce aminotransferases
  - Improve cardiovascular outcomes
- Statins are safe in NAFLD
  - No increased risk of hepatotoxicity
  - Can be safely used in compensated cirrhosis
  - Avoid in decompensated cirrhosis

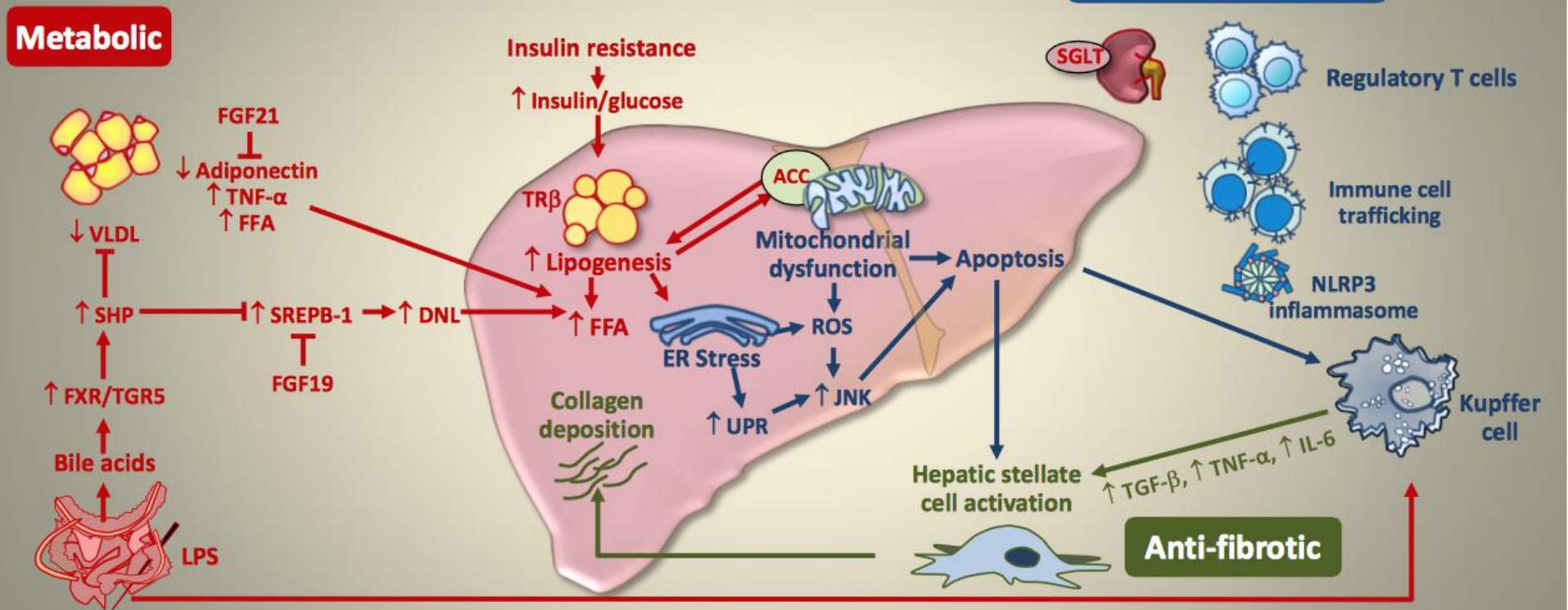
Chalasani N, et al. Hepatology 2018;67:328-357

Cardiovascular disease in NAFLD

AASLD Guidelines

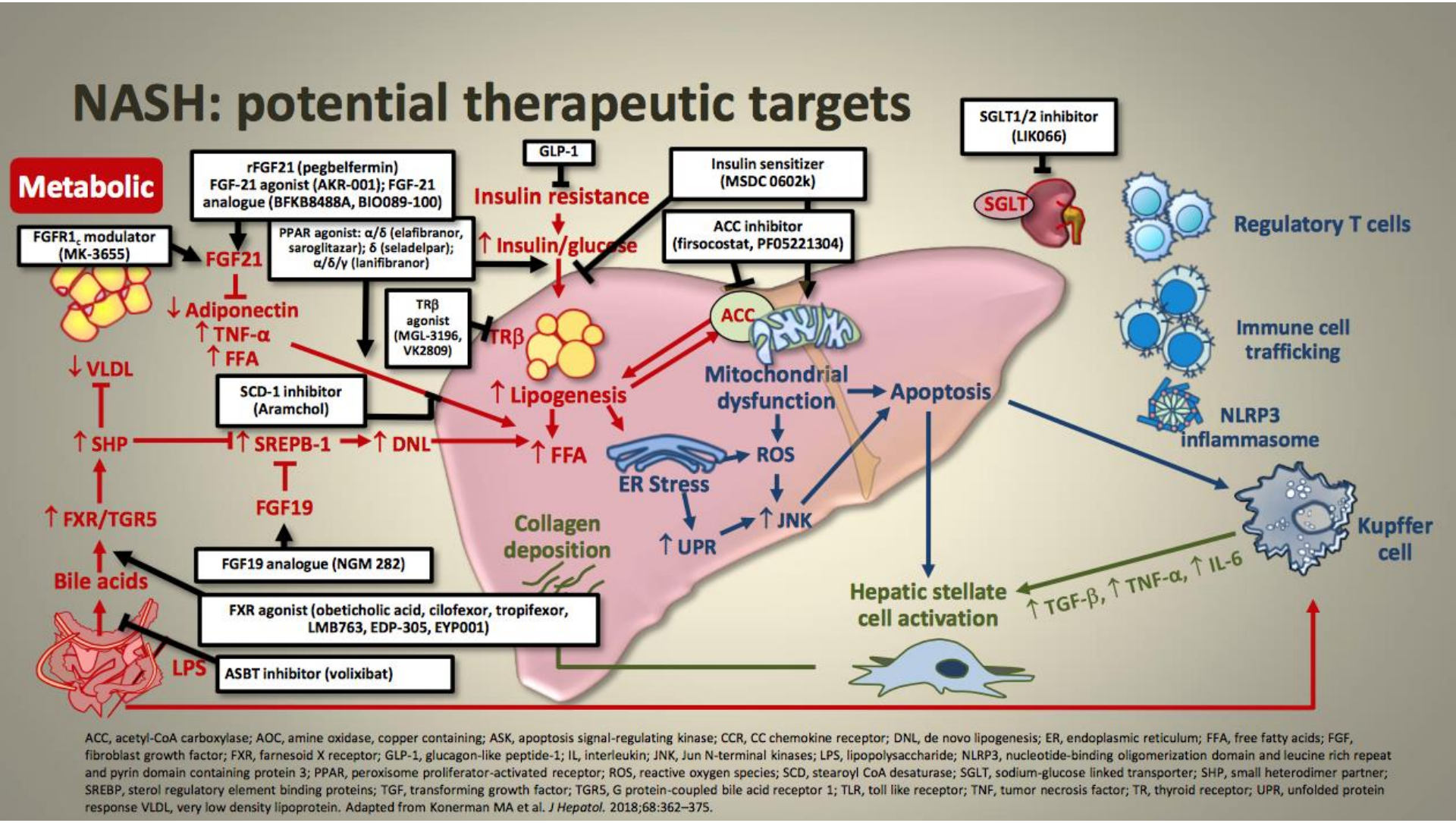
Statins can be used safely to treat dyslipidemia since there is no evidence that patients with CLD are at higher risk for serious liver injury than those w/o liver disease

NASH: potential therapeutic targets



ACC, acetyl-CoA carboxylase; AOC, amine oxidase, copper containing; ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acids; FGF, fibroblast growth factor; FXR, farnesoid X receptor; IL, interleukin; JNK, Jun N-terminal kinases; LPS, lipopolysaccharide; NLRP3, nucleotide-binding oligomerization domain and leucine rich repeat and pyrin domain containing protein 3; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SCD, stearoyl CoA desaturase; SGLT, sodium-glucose linked transporter; SHP, small heterodimer partner; SREBP, sterol regulatory element binding proteins; TGF, transforming growth factor; TGR5, G protein-coupled bile acid receptor 1; TLR, toll like receptor; TNF, tumor necrosis factor; TR, thyroid receptor; UPR, unfolded protein response VLDL, very low density lipoprotein. Adapted from Konerman MA et al. *J Hepatol.* 2018;68:362–375.

NASH: potential therapeutic targets



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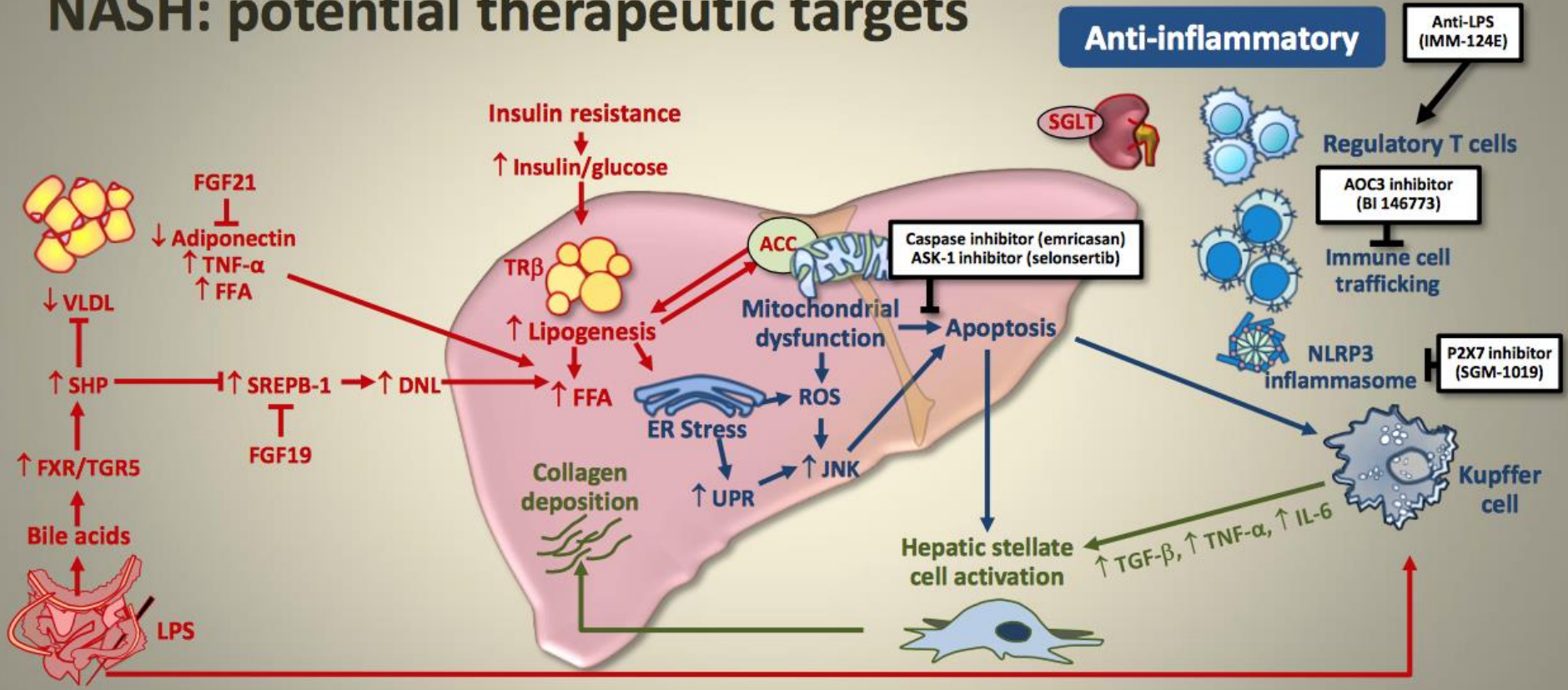

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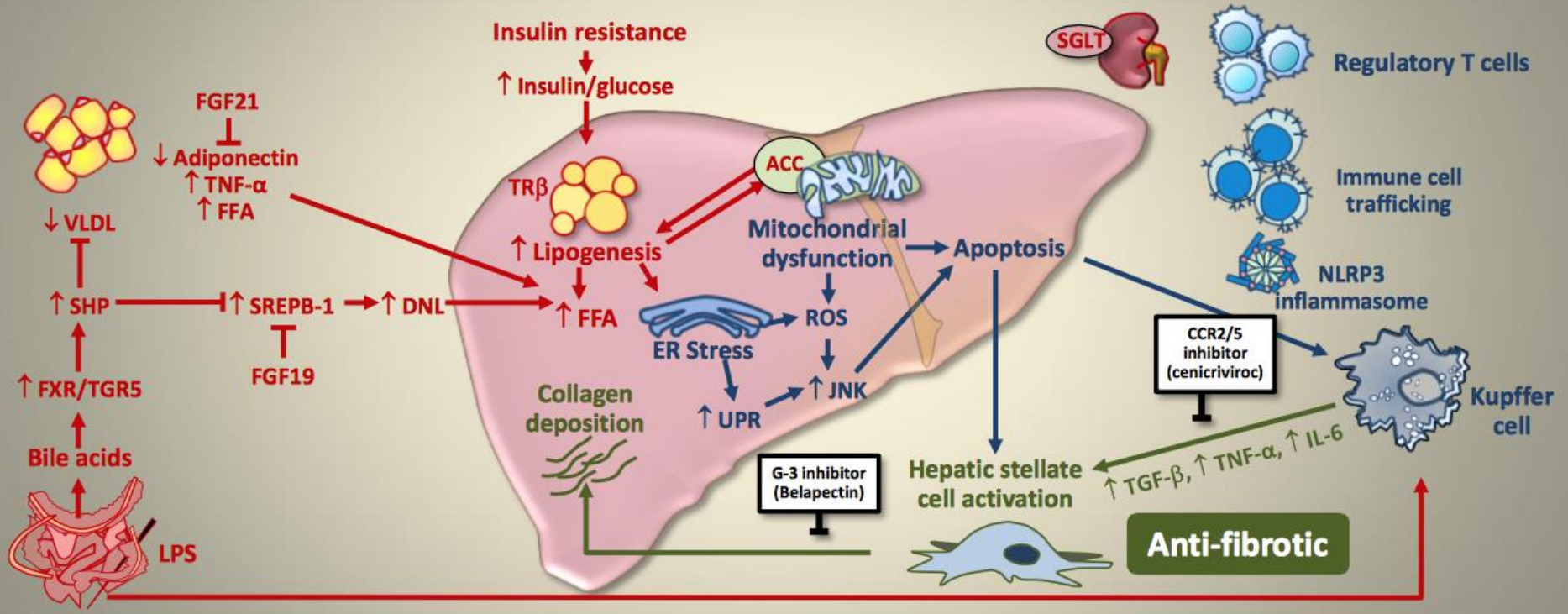
NASH: potential therapeutic targets



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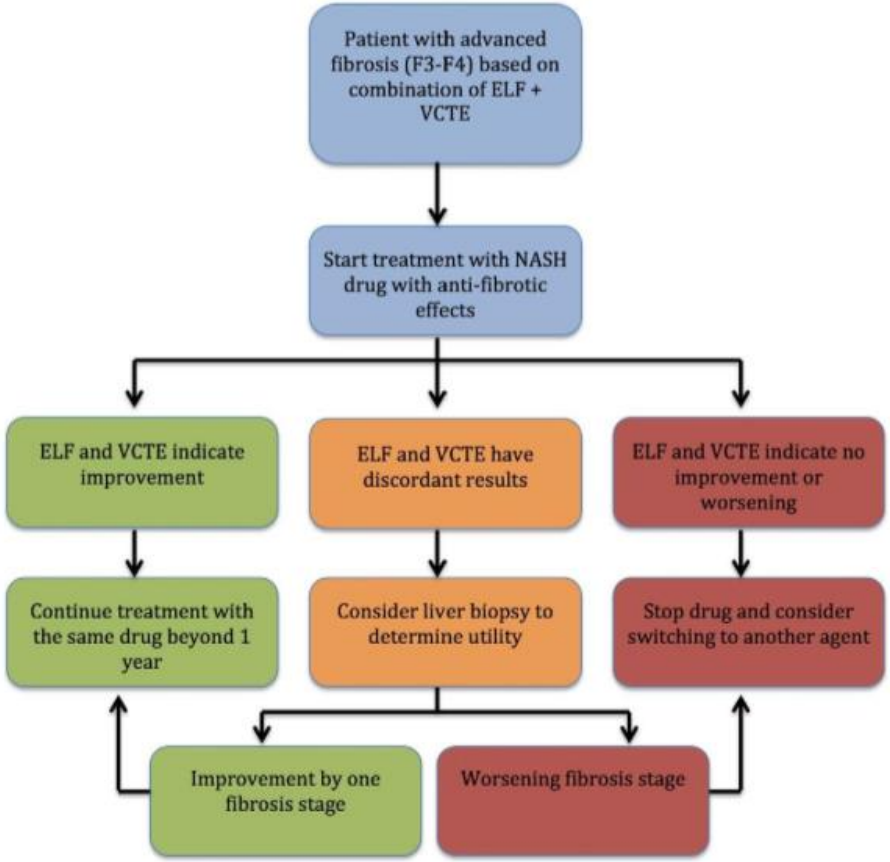
Regimens in Phase 3 Clinical Trials

- Obeticholic acid (FXR) met fibrosis endpoint and decrease in LFTs in phase 3 REGENERATE
- Cilofexor (nonsteroidal FXR agonist): met endpoint of significant reductions in hepatic steatosis
- Elafibranor (PPAR): did not meet NASH endpoint
- Selonsertib (ASK-1): did not meet fibrosis endpoint in cirrhotics Stellar 4 or bridging fibrosis Stellar 3
- Cenicriviroc (CCR2/CCR5) met only fibrosis improvement in Phase 2 CENTAUR, maintained for 2 years, phase 3 AURORA is on going
- NGM282 (analogue of FGF19): phase 2 trial with improvement in LFTs and hepatic steatosis

Proposed algorithm to determine treatment response to fibrotic NASH medications

- Start with a combination of highly accurate NITs
- Reassess in 1 year or longer
- You may add, stop or switch if no improvement
- You can assess periodically as these tests are east to do



Alkhouri, Lawitz and Noureddin; Hep Comm 2019

NAFLD and Liver Transplantation

Post-Liver Transplant Considerations in NAFLD Cirrhosis

- Recurrence of metabolic syndrome (39-40% at 5 yrs)
- Weight gain highest during first year
- Systemic hypertension in 70%
- Dyslipidemia in 2/3
- Chronic kidney disease increased by 4 fold if matched for other indications
- Frequency of coronary events increased by 50% when compared to other LT recipients
- Highest risk of death from cardiovascular or cerebrovascular disease is within 1 year of transplantation

Cotter TG, et al. Liver Transplantation 26 141-159 2020 AASLD

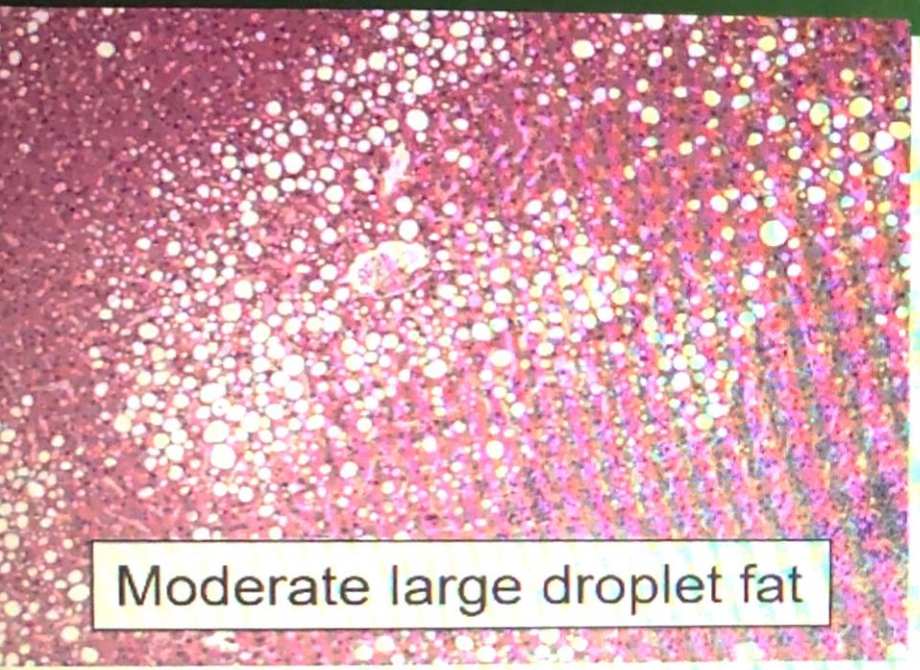
Covid-19 and NAFLD

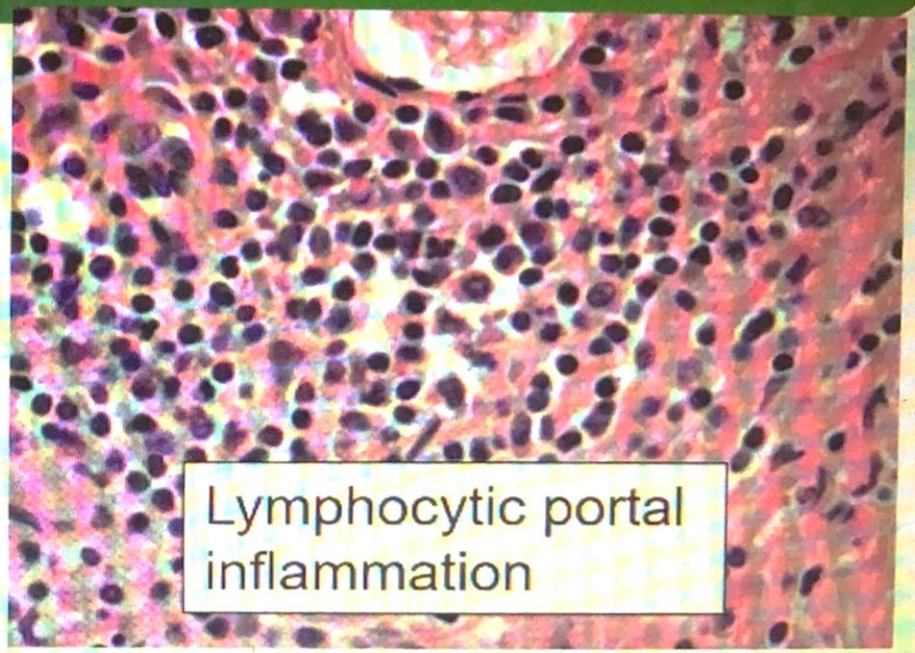
Covid 19 and NAFLD

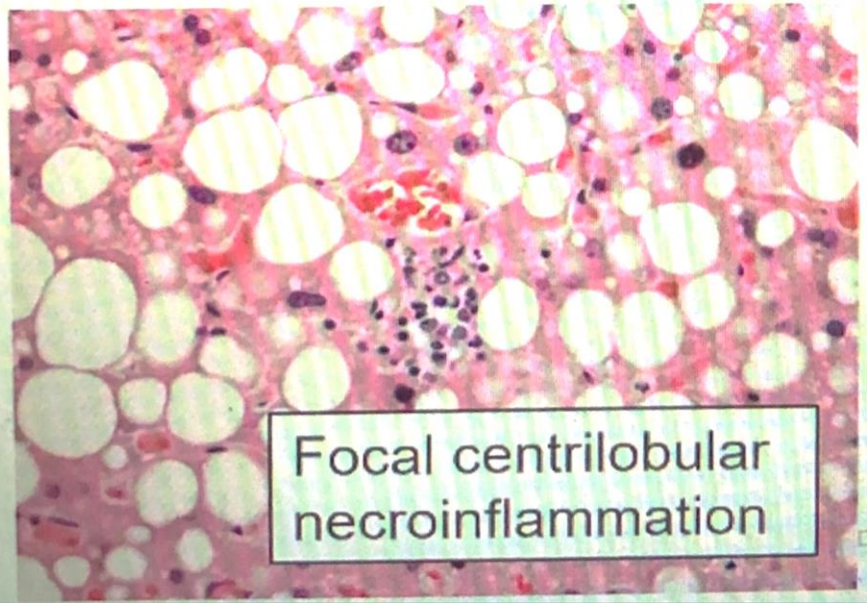
- Experience from NYC:
  - Report of more than 5000 patients
  - Most common comorbidities:
    - Hypertension
    - Diabetes
    - Obesity
    - Only 23% Hispanics (more likely to have NASH)
    - Highest mortality in African Americans (less likely to have NASH)

Autopsy Histology: AST 48, ALT 23

AASLD







- Overall changes most consistent with NAFLD
- Uncertain whether any of these represent COVID-specific changes

DY OF LIVER DISEASES

Courtesy of Jay Lefkowitch

COVID-19 and Liver Histology

- Not yet a complete description of liver histological changes with COVID-19
- Underlying disease (fatty liver or others) will impact liver enzymes and liver histology abnormalities
- Liver biopsy is not indicated unless there is strong suspicion for additional pathology that will influence urgent treatment decisions (allograft rejection)

Covid 19 and Liver

- Studies from China:
  - High prevalence of NAFLD among patients with severe Covid-19
  - Higher risk for progression to severe Covid-19
  - Longer viral shedding (17 vs 12 days)
  - Risk of obesity to Covid-19 severity is higher in those with NAFLD

Covid-19 and NAFLD

- Patients with NAFLD particularly those with diabetes and obesity should be considered high risk for Covid-19

Clinical Insights for Hepatology and Liver Transplant Providers During the Covid-19 Pandemic

https://www.aasld.org/about-aasld/covid-19-resources

Clinical Liver Disease, Vol 15, No 5, May 2020

Conclusions

- Prevalence of NASH amongst the US population is approximately 5% to 6% and is expected to increase markedly by 2030
- Fibrosis is a robust predictor of mortality and the development of end-stage-liver disease
- For some patients with advanced fibrosis (F3), progression to cirrhosis can be as rapid as 2.5 years
- NITs and imaging modalities such as fibroscan offer alternative ways to assess fibrosis and patients at risk for advanced fibrosis due to NASH
- Effective therapies that can halt or reverse fibrosis progression are urgently needed in order to prevent end stage liver disease
- Patients with NAFLD particularly those with diabetes and obesity should be considered high risk for Covid-19