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)

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.

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

**Metabolic**

- FGF21
- Adiponectin
- Insulin resistance
- ↑ Insulin/glucose
- ↓ VLDL
- ↑ SHP
- ↑ SREPB-1
- ↑ DNL
- ↑ FFA
- → Lipogenesis
- → Mitochondrial dysfunction
- → Apoptosis
- → ER Stress
- → ROS
- → JNK
- → UPR
- → TGF-β, ↑ TNF-α, ↑ IL-6
- Liver

**Anti-inflammatory**

- SGLT
- Regulatory T cells
- Immune cell trafficking
- NLRP3 inflammasome
- Kupffer cell

**Anti-fibrotic**

- LPS

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,脂多糖; 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

- 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 PILOYLOGICSTUDIO/SCIENCE PHOTO LIBRARY/Getty Images

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

- Increased BMI
- Obesity
- Metabolic syndrome
- Genetic factors
- Type 2 diabetes mellitus

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.
Assess for the Presence of the Metabolic Syndrome

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

Select Other Diseases That May Result in Steatosis/Liver Disease

- Non-alcoholic fatty liver (steatosis)
- Alcoholic liver disease
- Viral hepatitis
- Autoimmune Hepatitis
- Drug Induced Liver Injury
- Wilson’s Disease
- α₁-antitrypsin deficiency
- Hereditary hemochromatosis

As part of assessing a patient suspected of NASH, other diseases should be ruled out¹,²,a

¹This list of other liver diseases to exclude is not exhaustive.
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

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

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

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
### Nutrition Facts

<table>
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<th>% DV*</th>
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<tr>
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- **Percent Daily Values (DV)** are based on a 2,000 calorie diet.

- Not a significant source of Sat Fat, Trans Fat, Cholesterol, 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.

Kraft Foods North America, Inc.

Glenview, IL 60025 USA
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, 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 B₆), RIBOFLAVIN (VITAMIN B₂), THIAMIN HYDROCHLORIDE (VITAMIN B₁), VITAMIN A PALMITATE, BHT FOR FRESHNESS, FOLIC ACID, VITAMIN B₁₂, 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.
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*Percent Daily Values (DV) are based on a 2,000 calorie diet.

Not a significant source of Sat Fat, Trans Fat, Cholesterol, 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

KRAFT FOODS NORTH AMERICA, INC.
GLENVIEW, IL 60025 USA
Fibrosis: Predictor of Disease Progression and of Negative Outcomes
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.
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

- Controls
- F0
- F1
- F2
- F3
- F4

Log-rank $P < 0.001$

Follow-Up, years

Proportion Alive

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

- LSM Fibrosis classifications:
  - LSM₁ (F0/1)
  - LSM₂ (F1±1)
  - LSM₃ (F1/2)
  - LSM₄ (F2/3)
  - LSM₅ (F3±1)
  - LSM₆ (F3/4)
  - LSM₇ (F4)

Overall Survival

Follow-Up, years

Patients (n) 556

512 473 338 144

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.

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)

- NAFLD with cirrhosis (n=155)
- NAFLD with no cirrhosis (n=41)

% of all HCC cases

- 2000-2004: 8%
- 2005-2009: 12%
- 2010-2014: 15.9%

- 2000-2004: 5.5%
- 2005-2009: 3.2%
- 2010-2014: 2.7%

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

HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease; US = United States.
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\textsuperscript{1,2}

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
  - Haptoglobin
  - 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\(^2\)

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 identifying 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

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

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.

In this study, only 1 in 5 patients may achieve weight loss sufficient (≥7%) to significantly improve liver histology.

<table>
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<tr>
<td>Resolution of steatohepatitis, %</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
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<td>Fibrosis regression, %</td>
<td>16%</td>
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<td>Steatosis improvement, %</td>
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<tr>
<td>Patients achieving weight loss, %</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
<td>10%</td>
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</tbody>
</table>

Weight loss through lifestyle interventions can be difficult to sustain.


*Resolution of steatohepatitis was defined as absence of the histologic features of definite steatohepatitis, which required lack of hepatocellular ballooning with no fibrosis impairment.

Regression was defined as a decrease of at least 1 point in the fibrosis score. 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.
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

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

Antioxidants - Vitamin E

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

Insulin Sensitizers – Pioglitazone

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

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

Lewis JD, et al JAMA 2015;314:265-277
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

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

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

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

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

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

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

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 hypertriglycerideridemia in patients with NAFLD

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%

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

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

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

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

**Metabolic**
- Insulin resistance
  - ↑ Insulin/glucose
- Lipogenesis
  - ↑ FFA
- Mitochondrial dysfunction
  - → Apoptosis
- Collagen deposition
- Hepatic stellate cell activation
  - ↑ TGF-β, ↑ TNF-α, ↑ IL-6

**Anti-inflammatory**
- Anti-inflammatory
  - Regulatory T cells
  - Immune cell trafficking
  - NLRP3 inflammasome
  - Kupffer cell

**Anti-fibrotic**
- FGF21
  - ↓ Adiponectin
    - ↑ TNF-α
  - ↑ FFA
- TRβ
- ACC
- LPS
- SREPB-1
- ↑ DNL
- ↑ SHP
- ↑ FGF19
- ↓ VLDL
- ↑ FXR/TGR5
- Bile acids

**Legend**
- 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; TRH, 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

**Metabolic**
- FGFR1, modulator (MK-3655)
- FGF19
- FXR/TGR5
- Bile acids
- LPS
- ASBT inhibitor (volicitin)
- SCD-1 inhibitor (Aramchol)
- FGF19 analogue (NGM 282)
- FXR agonist (obeticholic acid, clofexor, tropifexor, LMB763, EDP-305, EYP001)
- PPAR agonist: α/δ (rosiglitazone, saroglitazone); δ (sildalide/gilpr); α/6/γ (levonorglax)
- FGFR1 agonist (AKR-001; FGF-21 analogue (BFK84884, B/0089-100))

**Insulin resistance**
- ↑ insulin/glucose
- ↓ insulin/glucose

**Lipogenesis**
- ↑ FFA
- ↓ FFA

**Mitochondrial dysfunction**
- ↓ ROS
- ↑ ROS

**Apoptosis**
- ↓ JNK
- ↑ JNK

**Hepatic stellate cell activation**
- ↑ TGF-β, ↑ TNF-α, ↑ IL-6

**Regulatory T cells**
- Immune cell trafficking
- NLRP3 Inflammasome
- Kupffer cell

**Inflammatory response**
- SGLT1/2 inhibitor (LTK066)

**Additional notes**
- 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
- FGFR: fibroblast growth factor
- FXR: farnesoid X receptor
- GLP-1: glucagon-like peptide-1
- IL: interleukin
- JNK: Jun N-terminal kinase
- LPS: lipopolysaccharide
- NLRP3: nucletotide-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
- TLR: toll like receptor
- TNF: tumor necrosis factor
- TR: thyroid receptor
- UPR: unfolded protein response
- VLDL: very low density lipoprotein

NASH: potential therapeutic targets

Anti-inflammatory
- Anti-LPS (IMM-124E)
- AOC3 inhibitor (BI 146773)
- P2X7 inhibitor (SGM-1019)

Insulin resistance
- FGF21
- Adiponectin

Lipogenesis
- VLDL
- FFA

Mitochondrial dysfunction
- ROS
- JNK

Apoptosis

Collagen deposition

Hepatic stellate cell activation

ER Stress
- UPR
- JNK

SREBP-1
- DNL
- FFA

FGF19
- SHP

Bile acids
- FXR/TGR5

LPS

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; GLP-1, glucagon-like peptide-1; 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-gluco 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;68:362–373.
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; GLP-1, glucagon-like peptide-1; IL, interleukin; JNK, Jun N-terminal kinases; LPS, lipopolysaccharide; NLRP3, nucleotide-binding oligomerization domain 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.
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 easy 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

- Moderate large droplet fat
- Lymphocytic portal inflammation
- Focal centrilobular necroinflammation

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

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

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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