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

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Asociación Puertorriqueña de Gastroenterología

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

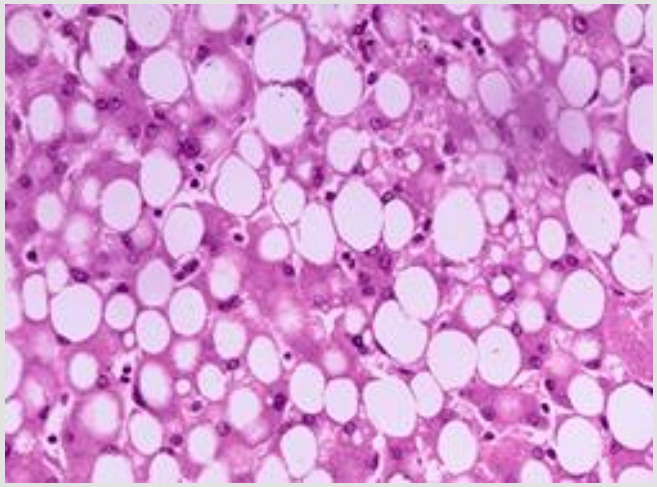
Examples of "standard drinks"
12 ounces of 5% alcohol beer
8 ounces of 7% alcohol malt liquor
5 ounces of table wine
1.5 ounces of distilled spirits (40% alcohol)

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

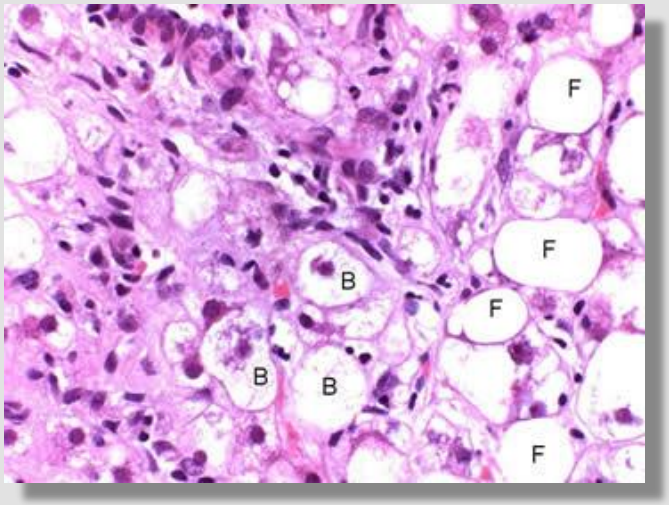
Non Alcoholic Fatty Liver Disease
NAFL vs NASH: Histologic Criteria

- **NAFL**:
  - Hepatic Steatosis
  - No evidence of Hepatocellular Injury (ballooning)
  - No evidence of Fibrosis

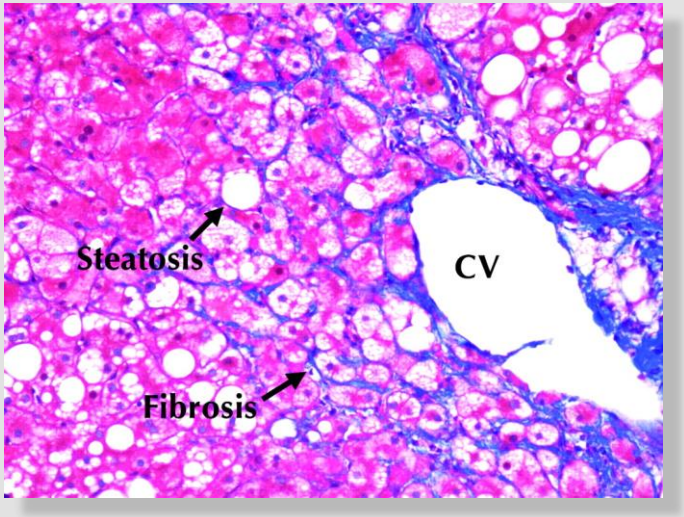
- **NASH**:
  - Hepatic Steatosis
  - Inflammation
  - Evidence of Hepatocellular Injury (ballooning)
  - Presence or Absence of Fibrosis



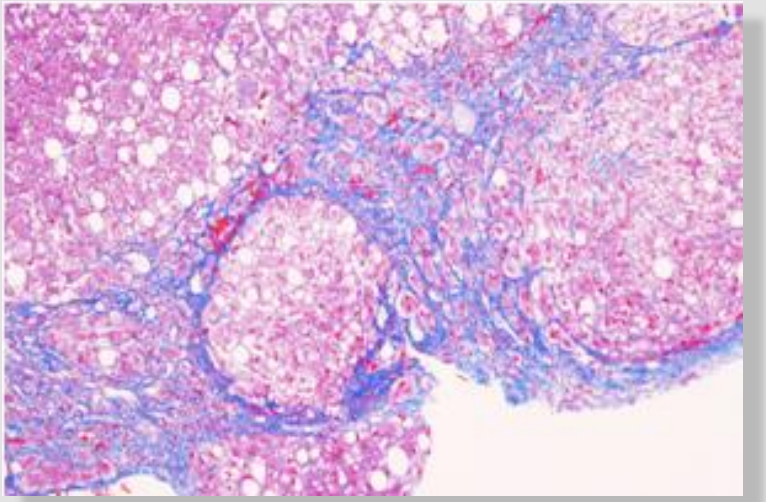
Fatty Liver



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**
  - **Over feeding**
  - **Obesity**

- **Diminished hepatic export of FFA**
  - **Accumulation of hepatocyte lipids leading to oxidative hepatocyte damage**

Pathogenesis of NAFLD

- Metabolic Factors
- Inflammatory Pathways
- Fibrosis
- Microbiome
- Genetic Factors

Pathogenesis of NASH: Metabolic Factors

Insulin resistance leads to attenuation of:

- **Peroxisome Proliferator-Activated Receptors**
  - **PPAR-α** reduces triglyceride levels
  - **PPAR-γ** causes insulin sensitization and enhances glucose metabolism
  - **PPAR-β/δ** enhances fatty acids metabolism
- **Farnesoid X nuclear receptor**: binds to lipophilic bile acids
  - promotes insulin sensitivity
  - decreases hepatic gluconeogenesis
  - Increases activity of SHP leading to attenuation of SREPβ-1

Pathogenesis of NASH: Metabolic Factors

Insulin Resistance leads to attenuation of:

- Glucose-dependent insulinotropic polypeptide (**GIP**)
  - **Stimulates insulin secretion** from pancreatic beta-cells
  - Found in intestinal cells

- Glucagon-like peptide-1 (**GLP-1**)
  - **Potentiates insulin secretion** after meal ingestion
  - Important role in glucose homeostasis
  - Reduces hepatic fat content
  - Found in cells of small intestine

Pathogenesis of NASH: Inflammatory Pathways

Activation of:

- **Apoptosis signal-regulating kinase** (**ASK1**):
  - Increases **inflammatory cytokines**
  - Up-regulates genes involved in fibrosis
  - Promotes apoptosis and cellular proliferation

- **Caspase 2**
  - activation leads to **cellular apoptosis**

Pathogenesis of NASH: Inflammatory Pathways

- Visceral Fat and Increased **cholesterol levels**
  - Lipotoxic trigger
  - Sensitizes hepatocytes to TNF alpha and Interleukin-6 (murine models)
  - Depletion of **mitochondrial glutathione** and **loss of mitochondrial integrity**

Pathogenesis of NASH: Microbiome

- Diets high in saturated fat and fructose alter **microflora**

- This results in **dysbiosis** with increased intestinal barrier permeability (diminished tight junctions and adherens junction proteins),
  - **bacterial translocation** and endotoxin production
  - activation of hepatic receptor induced **inflammation (iNOS expression, CYP2E1)**

Hepatology 2021;73:2180-2195

Pathogenesis of NASH: Fibrosis

- **Galectin-3**
  - Promotes fibrosis by **collagen deposition** and apoptosis

- **C-C chemokine receptor types 2 (CCR2) / 5 (CCR5)**
  - Promotes **fibrogenesis**
  - Monocyte/macrophage recruitment and tissue infiltration
  - **Hepatic stellate cell activation**

Pathogenesis of NASH: Genetic Factors

- Patatin-like phospholipase domain-containing gene (PNPLA-I148M)

- Experimental rat models:
  - In the presence of high sugar diet
  - Up regulation of ceramide metabolism (antagonizes insulin action)
  - ER stress/oxidative stress (p-JNK levels)
  - Activation of immune system: TNF, IL-6, STAT 1, Jak-STAT3
  - Microbial dysbiosis, intestinal barrier disruption, translocation of microbial products leading to activation of toll-like receptors
  - Activation of Hepatic Stellate Cells and collagen transcript levels
- Small interfering RNA-lipid nanoparticles can be used to silence PNPLA-3 expression and prevent NASH related fibrosis

Banini et al. Hepatology 2021;73:1290-1306

Diagnosis of NAFLD

Suspect NAFLD

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

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

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

AVOID INTAKE OF HIGH FRUCTOSE CORN SYRUP

Fatty Liver Risk Increases with Daily Intake of Sugary Drinks

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

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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FAT FREE MAYO 16 OZ


Bone
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).

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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: $1\frac{1}{2}$ 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

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

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*TRIVIAL SOURCE OF FAT AND CHOLESTEROL

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FAT FREE MAYO 16 OZ

NAFLD in Children and Women

Children and NAFLD

271 obese children with biopsy proven NAFLD completed food questionnaires

- 90% would drink sugary sodas several times per week
- 95% would consume one snack daily (crackers, pizza, cookies, yogurt, sweet snacks)
- > 40 gr fructose daily, >70 gr added sugar

Nobili, et al, Journal of Hepatology 2017

Women and NAFLD

- Increased risk for NAFLD after menopause has been observed
- Drop in estrogen levels after menopause leads to alterations in metabolic processes that cause hepatic fat accumulation
- Hormonal replacement therapy be a protective factor against NAFLD

Women and NAFLD

- Impact of female sex on incident CV events using Cox proportional hazards regression analysis
- Longitudinal Cohort Study (1997-2014), Minnesota
- NAFLD women develop CVD at younger age than women from general population
- Females with NAFLD may benefit from initiation of statin and low dose aspirin

Allen AM, et al.Am J Gastroenterol 2019;114:1764-1771

Fibrosis: Predictor of Disease Progression and of Negative Outcomes

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**

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

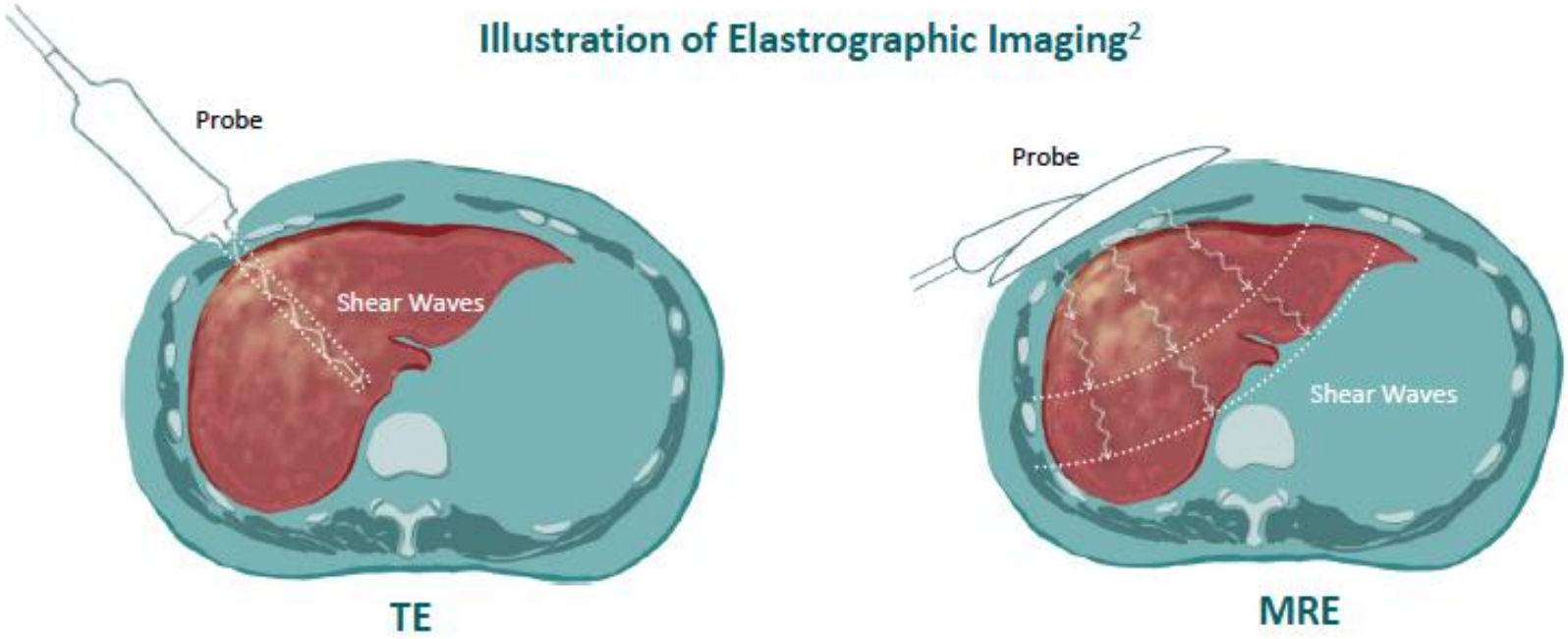
Noninvasive Diagnosis of Fibrosis in Adults with NAFLD

- 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

Fibrosis is a strong predictor of prognosis

- 20% of patients with NAFLD will develop NASH
- Hispanics with hepatic steatosis have about a 54% higher risk of fibrosis
- 11% of patients with fibrosis will develop cirrhosis in about 15 years
- 31% of patients with cirrhosis develop **decompensation over 8 years**
- 7% of patients with cirrhosis can develop **HCC in over 6.5 years**

Torres DM, et al. Clin Gastroenterol Hepatol. 2012,10(8):837-858.

Factors Associated with Fibrosis

- Framingham Heart Study:
  - Fibrosis is positively associated with obesity, metabolic syndrome, type 2 diabetes, hypertension, low HDL

  Long et al. Hepatology, Vol.73, No.2, 2021

- NHANES 2017-2018 Data:
  - Fibrosis is positively associated with HbA1c, waist circumference, systolic blood pressure and total cholesterol
  - Men with normal waist circumference have low chances of developing fibrosis even with hepatic steatosis

Any antifibrotic therapy is unlikely to be effective if glucose and body weight are not controlled

Fibrosis is a strong predictor of prognosis

- 1135 pts with **compensated cirrhosis** who had **failed** to simtuzumab (anti-Lysyl Oxidase-Like 2-inh. crosslinking of collagen fibers) and selonsertib (ACC inhibitor) trials
- **Baseline and 48 week** parameters:
  - Histologic scores (NASH CRN and Ishak)
  - Hepatic collagen and alfa-SMA expression (morphometry)
  - VCTE
  - Serum NITs: ELF, NAFLS Fibrosis Score, FIB-4
- **Risk of liver related clinical events lower in patients**:
  - Improvement in Ishak fibrosis score
- **Risk of liver related clinical events higher in patients**:
  - Increases in hepatic collagen, alfa-SMA, NFS and liver stiffness

Sanyal A et al. Abst 90. Hepatology, Volume 72, Number 1 (Suppl), 2020

Treatment of NASH

Goals of Treatment

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

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

Division of Hepatology and Nutrition at the FDA

Drugs used for treatment of NASH:

- For NASH with moderate or bridging fibrosis (F2 and F3):
  - Resolution of steatohepatitis and no worsening of liver fibrosis
  - Improvement in liver fibrosis greater than or equal to one stage and no worsening of steatohepatitis
  - Resolution of both steatohepatitis and improvement in fibrosis

Hepatology, Vol.73, No.5, 2021

Clinical Trial Endpoints

- Histologic improvement: liver biopsies required
- Serologic parameters:
  - ALT (10 u/L reduction associated with histologic resolution of NASH, >17 U/L reduction predicted histologic response)
  - FIB-4
  - NFS
  - ELF: hyaluronic acid, procollagen III amino terminal peptide, tissue inhibitory of matrix metalloproteinase
- Radiological parameters:
  - VCTE
  - MRI-PDFF (MRI proton density fat fraction)
- Combination of modalities
  - VCTE
  - MRI-PDFF (MRI proton density fat fraction)

Treatment

- Weight loss
- Lifestyle interventions
- Insulin Sensitizers
- Vitamin E
- GLP 1 agonists
- Ursodeoxycholic acid and Omega 3 fatty acids
- Bariatric Surgery/Endoscopic Interventions
- Novel Medications

Insulin Sensitizers-AASLD Guidance

1. Metformin may improve serum aminotransferases
2. Improves insulin resistance
3. No significant improvement in liver histology

Not recommended for treatment of NASH

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

PPARγ agonist (thiazolidinedione)– AASLD Guidance

1. In **biopsy proven NASH**, Pioglitazone (Actos) 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

Lanifibranor (pan PPAR)

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

GLP-1 Agonists – AASLD Guidance

1. Stimulate glucose dependent **insulin release**
2. Associated with weight loss
3. Liraglutide (Victoza)(**LEAN Study**) has shown improvement of NASH and decreasing rate of disease progression

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

Semaglutide associated with weight loss, normalization of LFT's and decrease in hepatic fat content

Chalasani N, et al. Hepatology 2018;67:328-357
Armstrong MJ et al. Lancet 2016:13:679-90
O'Neil PM et al.Lancet 2018;392:637-649

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

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 – 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

Novel Medications
AASLD 2020 Abstract Submissions

NASH Treatments Under Phase 2 or 3 Investigation

- Insulin Resistance and/or lipid metabolism:
  - PPARγ: Pioglitazone (Actos)
  - GLP1: Liraglutide (Victoza), Semaglutide (Ozempic)
  - SGLT: Empagliflozin (Jardiance), licogliflozin, canagliflozin (Invokana)
  - DPP4: Sitagliptin (Januvia)
  - ACC: GS0976 (Firsocostat), PF05221304
  - SCD1: Aramchol
  - ASBT: Volixibat

NASH Treatments Under Phase 2 or 3 Investigation

- Lipotoxicity and Oxidative Stress
  - PPAR$\alpha\delta$: Elafibranor
  - PPAR$\alpha\gamma$: Saroglitazar
  - Pan-PPAR: Lanifibranor
  - FGF19: NGM282 (Adalfermin)
  - FGF21: Pegbelfermin, Efruxifermin
  - FXR: OCA, Cilofexor, Tropifexor, Nidufexor
  - MPC: MSDC 0602K (second generation thiazolidinedione)
  - TGR5: INT 767/777
  - THRβ: Resmetirom/VK2809

NASH Treatments Under Phase 2 or 3 Investigation

- Inflammation and immune activation:
- CCR2/5: Cenicriviroc
- P2X7R: SGM-1019
- TLR4: JKB-121/122

NASH Treatments Under Phase 2 or 3 Investigation

- Cell Death (apoptosis and necrosis):
  - ASK1: Selonsertib
  - Caspase: Emricasan

NASH Treatments Under Phase 2 or 3 Investigation

- Fibrogenesis and collagen turnover:
  - Galectin: GR MD 02
  - LOXL2 (Lysyl oxidase like 2): Simtuzumab

Pharmacologic Treatment of NASH

- FXR agonist
- FGF 21 analog
- FGF19 analog
- Pan PPAR Agonist

Regenerate trial: 18-month interim efficacy analysis FXR Agonist: Lipotoxicity/Oxidative stress

- 2730 pts with **NASH (F1-3):**
  - Obeticholic acid 10 mg, 25 mg or placebo
  - **Significant Fibrosis improvement** (>1 stage with no worsening of NASH): 18% for 10 mg, 23% for 25 mg, 12% for placebo)
  - **No statistical difference for NASH resolution**
  - At present liver biopsies are **under revision** per request of FDA

Younossi Z et al. Lancet. 2019 Dec 14;394(10215):2184-2196

Efruxifermin (EFX): Balanced Phase 2a Study
FGF 21 analog: Metabolic/Lipotoxicity Stress

- 80 pts with biopsy proven **NASH F1-3**
- EFX 28 mg, 50 mg, 70 mg, placebo
- Endpoint: absolute change in liver fat measured by MRI-PDFF
- After 16 weeks of treatment:
  - **48% ≥ 1-STAGE fibrosis improvement with no worsening of NASH**
  - **48% NASH resolution with no worsening of fibrosis**
  - **28% ≥ 2 stage fibrosis improvement**
  - **Significant reductions in serum triglycerides and weight** and increase in HDL
  - Robust decrease in C-peptide (less insulin secretion)
  - Safe and generally well tolerated

Harrison S et al. Abst 8. Hepatology, Volume 72, Number 1(SUPPL), 2020

ALDAFERMIN Clinical Trial
FGF 19 analog (NGM282): Metabolic/Oxidative Stress

- Aldafermin 24 weeks vs placebo (once daily subcutaneous injection)
- 78 patients with biopsy-proven NASH with NAS≥4, **F2 or F3 fibrosis** and absolute liver fat content (LFC) ≥8%.
- MRI-PDFF and liver biopsies at baseline (BL) and W24
- Aldafermin produced greater reductions in fibrogenesis biomarker Pro-C3 in F3 patients than in F2 patients
- Compared with placebo, aldafermin had **greater effect in improving fibrosis in patients with NASH and advanced fibrosis (F3)**
- These data support further studies of aldafermin in patients with NASH and advanced fibrosis

Francque S et al. Abst LP9. Hepatology, Volume 72 1(Suppl),2020

Native Phase 2b Trial with Lanifibranor in Non-cirrhotic NASH pan-PPAR agonist: Metabolic/Lipotoxicity Stress

- Lanifibranor
  - well-balanced agonist of all 3 PPAR isotypes
  - Increases HDL-cholesterol and adiponectin
  - Decreases insulin resistance and triglycerides (TG)
- 247 pts treated for 24 weeks
  - 103 T2DM/144 non diabetics
  - **82% F2-3**
  - Reduction in fasting glycemia starting at week 4 and HbA1c starting at week 14
  - Median HDL-c increase was > 8%
  - Median TG decrease was > 20% from week 4 onwards
  - **Major improvement in fibrosis and in NASH resolution in both groups when compared to placebo**

Anstee Q. Abst. LP36. Hepatology, Volume 72 1(Suppl),2020

Different Pathways Combinations

- FXR Agonist + ACC Inhibitor + ASK1 Inhibitor
- GLP1 Agonist + FXR Agonist + ACC Inhibitor

ATLAS Study Phase 2 Clinical Trial
Combination of Pathways

- 48 week trial in **F3/F4**, compensated cirrhosis
- Individual and combination regimens of:
  - Cilofexor (30 mg): **non steroidal FXR agonist**
    - Increases FGF19 and decreases bile acid synthesis, lipogenesis, and gluconeogenesis
  - Firsocostat (20 mg): **allosteric inhibitor of acetyl coA carboxylase**
    - Inhibits rate limiting step in de novo lipogenesis
  - Selonsertib (18 mg): **inhibitor of ASK1** (apoptosis signal regulating kinase)
    - Inhibits inflammation and apoptosis

ATLAS Study Phase 2 Clinical Trial

- Results:
  - Firsocostat + Cilofexor:
    - **Improvement in non-invasive markers of fibrosis (from F3-F4 to ≤ F2)**
    - **Improvement in hepatic steatosis (MRI-PDFF)**
    - Highest rate of fibrosis regression: machine learning approach (ML approach)-automated and quantitative assessment of NASH

ATLAS Study Phase 2 Clinical Trial

- Side effects:
  - Pruritus 20-29%
  - Increase in VLDL
  - Decrease in HDL

Loomba R et al. Hepatology, Volume 73, Issue 2.Feb 2021.625-643

COMBINATION THERAPIES INCLUDING SEMAGLUTIDE (GLP-1 receptor agonist), CILOFEXOR (Farnesoid X receptor agonist), AND FIRSOCOSTAT (ACC inhibitor) IN Non-Cirrhotic PATIENTS WITH NASH Phase 2 Trial

- 108 non-cirrhotic patients with NASH (**F2-F3 on biopsy**, or MRI-PDFF ≥10% and liver stiffness by transient elastography [LS by TE] ≥7 kPa)
- sema (n=21), sema+CILO 30 mg (n=22), sema+CILO 100 mg (n=22), sema+FIR 20 mg (n=22), or sema+CILO 30 mg+FIR 20 mg (n=21) for 24 weeks (W24). CILO and FIR were taken once daily and sema subcutaneously once weekly (dose escalated from 0.24 mg to 2.4 mg weekly over 16 weeks)
- **Significant improvements in hepatic steatosis (MRI-PDFF) and ALT** in combination arms vs semaglutide alone
- **Liver stiffness and ELF declined in all groups but no difference between groups**
- Well tolerated, minimal GI effects

Alkhouri N et al. Abst L02. Hepatology. Volume 72, Number 1 (SUPPL),2020

Regimens in Phase 3 Clinical Trials

- Resmetirom (THR agonist) 2 pt reduction in NAS, **40% reduction in ALT** relative to placebo (Lancet Vol 394, 10213: 2012-2024, 2019)
- Namodenoson (A3AR agonist) (Inh inflam path leading to activation of stellate cells) significant decrease in ALT and MRI PDFF (Hepatology, Volume 72 1(Suppl),2020)
- Cenicriviroc (CCR2/CCR5) met **only fibrosis improvement** in Phase 2 CENTAUR, phase 3 AURORA is on going (Hepatology, Vol.67, No.5, 2018)
- Aramchol (inhibits stearoyl CoA desaturase modulator) reduced FA synthesis and improves insulin resistance (ARREST): **fibrosis improvement and significant decrease in LFT's** (Hepatology,AASLD Meeting 2019)
- MSDC-0602K (second generation thiazolidinedione) (binds MPC and modulates entry of pyruvate into mitochondria) improves insulin resistance (EMMINENCE trial) **significant decrease in NFS but not in fibrosis** (Hepatology, LO1, AASLD Liver meeting 2019)

Conclusions

- Prevalence of NASH amongst the US population is approximately 5% to 6% and is expected to increase markedly by 2030, driven by the increase in its risks factors, obesity, and diabetes
- Fibrosis is a 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
- Effective therapies that can halt or reverse fibrosis progression are urgently needed
- Ultimate goal of therapy is to prevent the development of end stage liver disease and its complications
- Medication therapy must be accompanied by lifestyle modifications