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

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Disclosure of Financial Relationships

Dawn M. Torres, MD

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

Research Grants/Contracts

Abbvie, Galectin, Gilead, Intercept, Conatus

Speaker’s Bureau

None
Objectives

- Describe the primary etiologies of chronic hepatitis today and predictions for the future face of liver disease
- Understand the criteria required for the diagnosis of NAFLD and NASH
- Outline the current available treatments for NAFLD and NASH
What is the most common chronic liver disease in the US?

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

Most common cause of liver disease globally. In U.S. prevalence is estimated at 30-40%
Case #1: 55 year old Hispanic female

- **ROS:** N/V/F/C. Occasional vague RUQ pain not assoc w/meals, BMs. No diarrhea, constipation, blood in stool.
- **+ ROS:** 20 lbs wt gain over 5 years
- **PMH:** DM Type 2, HTN, HLD, OSA, GERD
- **PSH:** Lap chole 2010 & TAH Hysterectomy 2005
- **Soc:** 1-2 drinks per week, no tobacco
- **Family History:** Grandmother with cirrhosis
- **Meds:** Metformin, Lisinopril/HCTZ, Atorvastatin, Aspirin, Prilosec
Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- **Physical exam:** HR 86, BP 137/80, RR 12, SPO2=98% RA, T 98.4, BMI 32.5
- Gen: Obese Hispanic female in NAD, A/Ox3, conversant & cooperative
- Lungs: CTA
- Cardio: RRR
- Abd: obese with well healed surgical scars. Liver palpable 3 cm below costal margin, spleen nonpalpable, nontender
- Extremities: no stigmata of liver disease, no pedal edema, no rashes
Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- **Basic labs:**
  - CBC: WBC 7, HCT 39, platelets 150
  - INR 1.0
  - Alk phos 80  AST 52  ALT 74  T bili 0.4
  - TP 7.8, Albumin 3.9
Case #1: 55 year old Hispanic female

- Helpful additional information:
  - Duration of liver enzyme elevation
  - Supplements or herbals
  - Risk factors for viral hepatitis – tattoos, IVDU or intra-nasal cocaine, high risk sexual behavior (anal intercourse, multiple partners), blood transfusion 1990s or earlier
  - Etiology of cirrhosis of grandmother
  - Health care maintenance: colonoscopy, pap/mammogram
Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- What is your differential diagnosis?
- What labs and imaging studies should be ordered?
- Is a liver biopsy indicated?
Differential diagnosis: asymptomatic mild-moderate hepatocellular liver enzyme elevation

- NAFLD
- Alcohol related liver disease
- Viral Hepatitis (B, C)
- Autoimmune hepatitis
- Drug induced liver injury
- Hemochromatosis
- Alpha-one anti-trypsin deficiency
- Thyroid dysfunction, Celiac
Case 1: Additional information

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

All pts with fatty liver

Liver biopsy

Isolated fatty liver

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

Increased risk: Cirrhosis & Liver cancer

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

- Cardiovascular disease
- OSA
- Vitamin D deficiency
- Diabetes
- PCOS
- Hypothyroidism
- Elevated ferritin
- Adenomatous polyps
- Hyperuricemia
- Pancreatic steatosis

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

Global Epidemiology of NAFLD

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

Abbreviations: N, North; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; S, South.
Natural History of NAFLD

- **Isolated Fatty Liver**
  - None to very minimal progression to fibrosis
  - No ↑ risk of death compared with the general population

- **Fatty Liver with Mild Inflammation**
  - Possible sampling variability with some risk of progression

- **NASH**
  - ↑ risk of death compared with general population
    - Cardiovascular, malignancy, liver-related
  - NASH with fibrosis portends worse prognosis
    - Fibrosis progression associated with diabetes, severe IR, weight gain >5 kg, rising ALT, AST
  - ~11% over 15 years, but significant variability

- **NASH Cirrhosis**
  - ~7% over 6.5 years

- **HCC**
  - ~31% over 8 years

- **Decompensation**

High risk patients

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

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

- Clinical or laboratory tests
  - NAFLD Fibrosis Score
  - FIB-4 index
  - BARD
  - AST/ALT ratio

- Imaging modalities
  - Shear-wave elastography
    - Fibroscan, Supersonic imaging, ARFI
  - MRE
  - MRI-based
    - Liver MultiScan

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

Online calculator

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

| Age (years) | |
| BMI (kg/m²) | |
| IGF/diabetes | [ ] |
| AST | |
| ALT | |
| Platelets (x10⁹/L) | |
| Albumin (g/L) | |

\[-1.675 + (0.037 \times \text{age[years]}) + (0.094 \times \text{BMI [kg/m}^2\text{]}]) + (1.13 \times \text{IFG/diabetes [yes =1, no = 0]}) + (0.99 \times \text{AST/ALT ratio}) – (0.013 \times \text{platelet[10⁹/L]}) – (0.66 \times \text{albumin[g/dL]})\]

[http://nafldscore.com](http://nafldscore.com)
### NAFLD Fibrosis Score

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

<table>
<thead>
<tr>
<th>Cutoff Point</th>
<th>Group</th>
<th>Predictive Value for Advanced Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low cutoff point:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;-1.455</td>
<td>Derivation</td>
<td>NPV 93%</td>
</tr>
<tr>
<td></td>
<td>Validation</td>
<td>NPV 88%</td>
</tr>
<tr>
<td>High cutoff point:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.676</td>
<td>Derivation</td>
<td>PPV 90%</td>
</tr>
<tr>
<td></td>
<td>Validation</td>
<td>PPV 82%</td>
</tr>
</tbody>
</table>

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

Transient Elastography

- FibroScan® = patented technology Vibration Controlled Transient Elastography (VCTE™)

- Two quantitative parameters:
  - Liver stiffness expressed in kPa
    ➔ Correlated to liver fibrosis [1]
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    ➔ Correlated to liver steatosis [2]

- Volume of liver tissue (3cm³)
  - 100 times bigger than liver biopsy

[FibroScan® 502 TOUCH]
Case 1: Additional information

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

- **Fibroscan:** 9 kPascals
Liver biopsy: Stage 3 NASH

Case 1: Stage 3 NASH...Now what?

- What is the optimal treatment for NAFLD patients?
  - **Diet/exercise**
    - Surgical
    - Pharmacotherapy
Pathogenesis of NASH with Potential Sites for Therapy

NAFLD: Dietary Characteristics

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

2. Zelber-Sagi S, J Hepatol 2007
4. Ackerman Z et al, Hypertension. 2005
Weight Loss

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

Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies

- Weight loss ≥ 10%
  - Fibrosis regression (45% of pts)

- Weight loss ≥ 7%
  - NASH resolution (64% to 90% of pts)*
  - Ballooning/inflammation (41% to 100% of pts)*

- Weight loss ≥ 5%
  - Steatosis (35% to 100% of pts)*

*Depending on degree of weight loss.

Exercise

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

- Duodenal switch procedure
- Adjustable gastric banding
- Roux-en-Y gastric bypass
- Gastric sleeve
# Bariatric Surgery for Adult NAFLD

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

Bariatric Surgery

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

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

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

Diabetic medications

- Thiazolidinediones (TZDs)
  - Avandia
  - Actos
- Metformin
- Incretin mimetics
Pioglitazone

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

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

Pioglitazone

- The pro’s
  - ↓ insulin resistance
  - Improves hepatic histology albeit modest fibrosis benefit
  - Previous concerns of bladder cancer likely unwarranted\(^1\)

- The con’s
  - Weight gain (5-10 pounds)
  - Bone fractures in diabetics\(^2\)
  - CHF Black box warning (rare)
  - Benefits short-lived after discontinuation of therapy

Pioglitazone

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

\(^1\)Chalasani N et al. Gastroenterology 2012;142:1592-1609.
Metformin

• Biguanide improves insulin sensitivity
  • Decreases hepatic gluconeogenesis
  • Limits triacylglycerol production
• Promising animal studies
• Adult & pediatric NAFLD
  • Improves hepatic steatosis
  • No significant improvement in fibrosis & necroinflammation
Incretin mimetics and enhancers

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

Vitamin E

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

\(^1\)Sato K et al. Nutrition 2015;31:923-930
## Major studies with histologic endpoints

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</thead>
<tbody>
<tr>
<td>Harrison 2003</td>
<td>6 months</td>
<td>Vit E 1000 IU/d &amp; Vit C 1000 mg/d</td>
<td>25+24</td>
<td>Vit E/C superior to placebo for fibrosis score but NOT inflammation/necrosis</td>
</tr>
<tr>
<td>Sanyal 2010 (PIVENS)</td>
<td>96 weeks</td>
<td>Vit E 800 IU/d</td>
<td>84+83</td>
<td>Vit E improved ballooning, NAS, no Δ fibrosis</td>
</tr>
<tr>
<td>Lavine 2011 (TONIC)</td>
<td>96 weeks</td>
<td>Vit E 800 IU/d</td>
<td>58+58</td>
<td>Vit E improved NAS, induced resolution of NASH (58% v 28%)</td>
</tr>
</tbody>
</table>

Meta-analysis Vitamin E versus placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>0.93 (0.79, 1.09)</td>
</tr>
<tr>
<td>Ballooning degeneration</td>
<td>0.73 (0.61, 0.81)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>0.73 (0.59, 0.89)</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
<td>0.82 (0.62, 1.09)</td>
</tr>
</tbody>
</table>

Vitamin E Potential Risks

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

$^{3}$Klein EA et al. JAMA 2011;306,1549-56.
Vitamin E

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

\(^1\)Chalasani N et al. Gastroenterology 2012;142:1592-1609.
Pentoxyfylline

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

1Li W et al. Lipids Health Dis 2011;10:49.
## Pentoxyfylline (PTX)

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

Pentoxyfylline

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

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

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

- Many NAFLD patients meet tx guidelines for statin therapy for CV benefit:
  - NAFLD pts also have ↑ LAEs, statins may further ↑ LAEs but RARELY cause serious liver disease

- STATINS ARE SAFE TO USE IN NAFLD/NASH\(^1\)

\(^1\)Chalasani N et al. Gastroenterology 2012;142:1592-1609.
Statins

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

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

Investigational therapies

- **Anti-fibrotic**
  - Simtuzumab → Study terminated for lack of efficacy

- **Anti-inflammatory**
  - Elafibranor
  - Cenicriviroc
  - Galectin-3 antagonists
  - NOX-1 and NOX-4 inhibitors

- **Hepato-protective**
  - Farnesoid X nuclear receptor ligand
  - PPAR-α/δ agonist
  - Pan-caspase protease inhibitor

Noureddin M et al. AP&T. June 2016
Obeticholic acid (OCA) 
(Farnesoid X nuclear receptor ligand)

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

Risk Stratification in Pts With Suspected NAFLD

Hepatic steatosis on imaging ± elevated serum ALT levels

- Evaluate alcohol consumption
- Confirm NAFLD
- Exclude alternate causes of ↑ALT levels

Low-risk profile
- BMI < 29.9
- Age < 40 yrs
- No T2DM or metabolic syndrome features
- Noninvasive fibrosis estimation:
  - FIB-4 < 1.30
  - APRI < 0.5
  - NFS < -1.455
- FibroScan < 5 kPa

Intermediate-risk profile
- BMI > 29.9
- Age > 40 yrs
- Multiple features of the metabolic syndrome
- Noninvasive fibrosis estimation:
  - FIB-4 1.30-2.67
  - APRI 0.5-1.5
  - NFS -1.455-0.675
- FibroScan 6-11 kPa

Follow and reassess as risk factors evolve

Intermediate-risk profile
- AST level > ALT level
- Platelets < 150,000
- Noninvasive fibrosis estimation:
  - FIB-4 > 2.67
  - APRI > 1.5
  - NFS > 0.675
- FibroScan > 11 kPa

High-risk profile
- AST level > ALT level
- Platelets < 150,000
- Noninvasive fibrosis estimation:
  - FIB-4 > 2.67
  - APRI > 1.5
  - NFS > 0.675
- FibroScan > 11 kPa

Consider liver biopsy or confirmatory testing for cirrhosis (eg, MRE)

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- Evaluate alcohol consumption
- Confirm NAFLD
- Exclude alternate causes of ↑ALT levels

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- BMI < 29.9
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- No T2DM or metabolic syndrome features
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- FibroScan < 5 kPa

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Consider liver biopsy

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- AST level > ALT level
- Platelets < 150,000
- Noninvasive fibrosis estimation:
  - FIB-4 > 2.67
  - APRI > 1.5
  - NFS > 0.675
- FibroScan > 11 kPa

Consider liver biopsy or confirmatory testing for cirrhosis (eg, MRE)
Treatmet of NAFLD based on liver histology

- Isolated fatty liver disease
  - Manage metabolic risk factors
  - No increased risk of liver related morbidity/mortality

NASH

Non-diabetic with < stage 2 fibrosis:
- 1-2 cups of coffee daily
- Dietary modification (increased PUFA/MUFA) and exercise
- Weight loss of 20% total body weight
- Treat hyperlipidemia with a statin or ezetimibe

Consider:
- Vitamin E 800 IU daily
- Orlistat, lorcaserin or phentermine/topamax as an adjunct for weight loss
- Clinical trials

Non-diabetic with > stage 2 fibrosis:
- 1-2 cups of coffee daily
- Dietary modification (increased PUFA/MUFA) and exercise
- Weight loss of 5-10% total body weight
- Treat hyperlipidemia with a statin or ezetimibe

Consider:
- Vitamin E 800 IU daily
- Orlistat, lorcaserin or phentermine/topamax as an adjunct for weight loss
- Bariatric surgery if comorbidities
- Clinical trials

Diabetic with any stage of fibrosis:
- 1-2 cups of coffee daily
- Dietary modification (increased PUFA/MUFA) and exercise
- Weight loss of 20% total body weight
- Treat hyperlipidemia with a statin or ezetimibe

Consider:
- Metformin, pioglitazone or rosiglitazone
- Exenatide or liraglutide (as treatment for diabetes)
- Orlistat, lorcaserin or phentermine/topamax as an adjunct for weight loss
- Bariatric surgery if comorbidities
- Clinical trials

Investigational Medications:
- Simtuzumab
  - Anti-fibrotic
- Anti-inflammatory/Metabolic
  - Elafibranor
  - Aramchol
  - Cenicriviroc
- Obeticholic acid (not commercially available)

More research needed prior to recommending:
- Pentoxyfylline
- ARBS
- Vitamin C
- Betaine

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

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