Nonalcoholic Steatohepatitis: Evaluation and Management

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A patient presents to you for evaluation of “elevated liver enzymes”

A 57 yo F with a history of impaired fasting glucose, hypertension and dyslipidemia

USOH until 3 months ago when she developed an “achy” RUQ pain. After the pain persisted for 3 weeks, she went to the local ER for evaluation

LFTs showed ALT 85, AST 65, normal AP, GGT, TB, albumin, normal CBC, BMP, UA, Abdominal US showed “heterogeneous liver echotexture”, normal GB, no kidney stones

Her pain has resolved but she now presents for further evaluation of the US findings and elevated transaminases
Based on this history, what is the most accurate description of her presentation?

1. She has nonalcoholic fatty liver disease (NAFLD)
2. She has nonalcoholic fatty liver (NAFL)
3. She has nonalcoholic steatohepatitis (NASH)
4. She has NASH cirrhosis
5. None of the above
Based on this history, what is the most accurate description of her presentation?

**NAFLD:** refers to the entire spectrum of fatty liver disease in individuals without significant alcohol use, ranging from fatty liver ("simple steatosis"), nonalcoholic steatohepatitis, to cirrhosis

**NAFL:** 5% or more hepatic steatosis without hepatocyte ballooning or fibrosis with low risk of progression to cirrhosis

**NASH:** 5% or more steatosis with inflammation, ballooning with or without fibrosis, which can progress to cirrhosis/HCC/liver failure

**NASH cirrhosis:** Presence of cirrhosis with histological evidence of steatosis or steatohepatitis

**Cryptogenic cirrhosis:** Presence of cirrhosis without obvious etiology. Commonly patients exhibit obesity and metabolic syndrome

AASLD NAFLD Guidance, 2017
NAFL ("not-NASH") has good prognosis
Nonalcoholic steatohepatitis (NASH) can progress
NASH is characterized by chicken-wire pattern of fibrosis
Based on her presentation, you suspect she likely has NAFLD

Which of the following is the currently favored hypothesis regarding the pathogenesis of NAFLD?

1. Adipose tissue dysfunction and adipoIR hypothesis
2. Obesity and insulin resistance hypothesis
3. Two hit hypothesis: 1\textsuperscript{st} hit is development of steatosis, 2\textsuperscript{nd} hit triggers inflammation
4. Multi-hit hypothesis: Multiple factors and steps are involved
NAFLD has a complex “multihit” pathogenesis involving genetics and multiple organ systems

Mann et al 2016
You obtain further information from the patient about her medical history

**PMH:** Impaired fasting glucose, dyslipidemia, hypertension, PCOS, menopause at age 48. Sleep study was negative for OSA at age 50. Unremarkable surgical history.

Besides her current comorbid problems, which other condition has been associated with NAFLD?

1. Fibromyalgia
2. Osteoarthritis
3. Psoriasis
4. Osteoporosis
5. All of the above
You obtain further information from the patient about her medical history

<table>
<thead>
<tr>
<th>Common conditions with established associations:</th>
<th>Other associated conditions:</th>
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</thead>
<tbody>
<tr>
<td>• Obesity</td>
<td>• Hypothyroidism</td>
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<tr>
<td>• T2DM</td>
<td>• OSA</td>
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<tr>
<td>• Dyslipidemia</td>
<td>• Hypopituitarism</td>
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<td>• Metabolic syndrome</td>
<td>• Hypogonadism</td>
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<tr>
<td>• PCOS</td>
<td>• Pancreato-duodenal resection</td>
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<td></td>
<td>• Psoriasis</td>
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</table>
You obtain further information from the patient about her family history

**FH:** Mother diagnosed with cirrhosis at 65 and died from sepsis at 70 (“she did not drink a drop of alcohol”), father alive at 79, has hypertension, and sister is 50 with T2DM and “high liver tests”

The patient states that she is “very worried” that she has increased risk of dying from liver disease because of her FH.

Which of the following is most accurate about heritability of NAFLD?

1. She has no increased risk of liver disease compared with the general population
2. Her FH increases her risk of having hepatic steatosis but not NASH by 25%
3. Her FH increases her risk of having advanced fibrosis by over 10-fold
4. Her FH increases her risk of developing HCC
First-degree relatives of individuals with NASH-cirrhosis have increased risk of advanced fibrosis

Caussy et al, JCI, 2017
The patient asks you whether her “genes” may be playing a role in her liver disease

Based on current evidence, what should you tell her?

1. Genome-wide association studies have repeatedly failed to identify NAFLD-associated polymorphisms
2. NAFLD-associated polymorphism identified so far are also associated with increased risk of T2DM
3. A gene has been identified that significantly increases risk of developing cirrhosis
4. She should undergo genetic testing for risk stratification given her strong family history of liver disease
Genetic susceptibility is involved in the pathogenesis of NAFLD

NAFLD assessed by abdominal CT-scan in population-based studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIANT, MAGIC, GOLD Consortium Population-based study</td>
<td>6629 European ancestry</td>
<td>~27%</td>
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<tr>
<td>Speliotes et al. 2011</td>
<td></td>
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<tr>
<td>IRAS Family Study</td>
<td>1142 Hispanics and African Americans</td>
<td>~31%</td>
</tr>
<tr>
<td>Wagenknecht et al. 2009</td>
<td></td>
<td></td>
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<tr>
<td>JHS, ARIC, GENOA, FamHS, IRASFS-Study Population-based study</td>
<td>3973 Hispanics and African Americans</td>
<td>~22-34%</td>
</tr>
<tr>
<td>Palmer et al. 2013</td>
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</table>

NAFLD assessed by liver biopsy, MRS or liver US in family-based or twin-studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial aggregation study. Hospital-based</td>
<td>11 controls/33 NAFLD.</td>
<td>~38%</td>
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<tr>
<td>Schwimmer et al. 2009</td>
<td></td>
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<tr>
<td>The Genetics of NAFLD in Twins Consortium Hospital-based Sample size: 60 pairs of twins (42 monozygotic and 18 dizygotic). MRI-PDF/ MRE Ethnicity: mixed</td>
<td>~50%</td>
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<tr>
<td>Loomba et al. 2015</td>
<td></td>
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<tr>
<td>Twin-study Hospital-based Sample size: 208 adult Hungarian twins (63 monozygotic and 41 dizygotic pairs). NAFLD: liver US</td>
<td>~74.2% and 25.8%</td>
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<tr>
<td>Tarnoki et al. 2012</td>
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Sookoian and Pirola, 2017
Much of the genetic variation underlying NAFLD heritability has not been identified.
Polymorphisms in the PNPLA3 and TM6SF2 genes increase susceptibility to progressive NASH

PNPLA3 I48M:
Increased NASH risk
independently of MetS

TM6SF2 I67K:
Increased NASH risk
Decreased CVD risk

Dongiovanni et al 2015
Wainwright and Byrne 2016
You obtain her social and substance use history

**SH:** She has never smoked or used drugs, drinks 6-7 per week, usually a glass of wine with dinner, she has two cups of coffee in the morning. She asks you about your recommendations about her alcohol and coffee consumption. Based on current recommendations, what do you suggest to her?

1. Continue both, there is no risk or benefit
2. Stop both, there is clear harm with both
3. Continue coffee, stop alcohol completely
4. Stop coffee, continue moderate alcohol
5. Continue coffee, role of moderate alcohol use is unclear
Coffee consumption is associated with reduction in risk of fibrosis in NASH patients

\[ y = -0.0006x + 1.5818 \]
\[ R^2 = 0.0312 \]

Molloy et al, Hepatology, 2011
Recommendations regarding alcohol use are not well defined

2017 AASLD NAFLD Guidance
- Patients with NAFLD should avoid “heavy” amounts of alcohol
- Insufficient data to make recommendations about “nonheavy” consumption

Definition of “significant alcohol consumption”
Men: > 21 standard drinks per week
Women: >14 standard drinks per week

DAFLD/DASH: Dual-etiology fatty liver disease (when ALD and NAFLD risk factors coexist)
You perform a physical examination

Exam: BMI 28.5, WC 38 inches, skin tags on the neck, no hepatomegaly, mild RUQ tenderness to deep palpation, otherwise normal

All of the following are true, EXCEPT:

1. Her central obesity increases risk of NAFLD
2. The skin tags on the neck suggest insulin resistance
3. If her BMI was 25, NASH would be unlikely on a liver biopsy
4. If she had spider angiomata on the neck, you would suspect underlying liver cirrhosis
A significant percentage “lean” NAFLD patients may have NASH

Biopsy-proven NAFLD
143/669 were lean
17% NASH prevalence in lean subjects versus 40% in subjects with obesity

Adapted from Fracanzani et al, Clin Gastro Hep, In press
You get further workup for her liver disease

Labs results shows ANA titer of 1:80, ASMA 1:20, ferritin 400 and normal ceruloplasmin. HCV/HBV serologies are negative. What is the implication of positive autoimmune antibodies in NAFLD?

1. Positive antibodies suggested autoimmune hepatitis superimposed on NASH
2. Positive antibodies are associated with increased risk of advanced fibrosis
3. Positive autoantibodies are associated with more rapid fibrosis progression to cirrhosis in NASH patients
4. There is no clinical significance. It is an epiphenomenon
Presence of autoantibodies is not associated with increased risk of NASH/fibrosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis (≥34 vs. &lt;34%)</td>
<td>0.58 (0.41–0.82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lobular inflammation (≥2 vs. &lt;2 under 20× mag)</td>
<td>0.90 (0.63–1.27)</td>
<td>0.53</td>
</tr>
<tr>
<td>Portal chronic inflammation (mild/more than mild vs. none)</td>
<td>0.98 (0.60–1.61)</td>
<td>0.95</td>
</tr>
<tr>
<td>Ballooning (few/many vs. none)</td>
<td>0.88 (0.62–1.27)</td>
<td>0.51</td>
</tr>
<tr>
<td>Fibrosis (any vs. none)</td>
<td>1.08 (0.71–1.63)</td>
<td>0.73</td>
</tr>
<tr>
<td>Fibrosis (advanced vs. mild/moderate/none)</td>
<td>1.30 (0.88–1.91)</td>
<td>0.19</td>
</tr>
<tr>
<td>NAFLD Activity Score (≥5 vs. ≤4)</td>
<td>0.76 (0.54–1.08)</td>
<td>0.13</td>
</tr>
<tr>
<td>NASH (definite/borderline vs. none)</td>
<td>0.87 (0.58–1.30)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Vuppalanchi, Liver Int, 2011
Based on this presentation, what should you do next?

1. She likely has alcoholic fatty liver. Recommend alcohol cessation and repeat labs in 3m
2. She likely has NAFLD. Ask her to lost 5-10% weight through diet and exercise and repeat US/labs in 3m
3. Check HCV, HBV, autoimmune markers, ferritin, ceruloplasmin
4. She likely has NASH, recommend a liver biopsy asap
5. She likely has NASH. Start vitamin E 400 Int. units/d
1. In suspected NAFLD, it is essential to rule out competing etiologies and coexisting common chronic liver diseases (HCV, HBV, autoimmune, hemochromatosis, Wilson’s, A1AT deficiency, and alcohol).

2. Vitamin E therapy is currently not recommended for patients with diabetes, without liver biopsy diagnosis of NASH, or cirrhosis.
NAFLD can be associated with conditions other than obesity/metabolic syndrome

**GENETIC**
- Abetalipoproteinemia
- Weber-Christian disease
- Galactosemia
- Type 1 glycogen storage disease
- Wilson’s disease
- Tyrosinemia
- Limb dystrophy
- Systemic carnitine deficiency

**NUTRITIONAL/INTESTINAL**
- Surgical: J-I bypass, B-P diversion
- TPN
- Rapid weight loss
- Severe protein calorie malnutrition
- IBD
- Jejunal diverticulosis with bacterial overgrowth

**DRUGS/TOXINS**
- Amiodarone
- Methotrexate
- Tamoxifen/synthetic estrogens
- Glucocorticoids
- Nucleoside analogs
- Calcium channel blockers
- Organic solvents
- Petrochemicals
Proposed simplified diagnostic workflow for NAFLD

M: ALT>30; F > 19
Repeat labs: Risk factors

Alcohol history, HBsAg, HCV Ab, ferritin/iron sat, ANA, ASMA, ASMA, AIAT level, ceruloplasmin

Treat as appropriate

Abd US echobright
Liver screen negative

NAFLD

NAFLD Fibrosis score
VCTE/Fibroscan

Low risk:
NFS<-1.455 (NPV 93%)
VCTE < 5 kPa*

PCP follow up/3 years
Reassess in 1 year
Lifestyle mod.

Indeterminate
NFS -1.455-0.676
VCTE 7-12.5*
OR Discordant NFS/VCTE

Liver biopsy
Treat if F2-3 fibrosis

High risk
NFS > 0.676 (PPV 90%)
VCTE > 12.5 (+/-1) kPa*

Manage as cirrhosis

*Cutoffs not validated
The patient is “afraid of needles” and would like to avoid a liver biopsy

You recommend initial evaluation with noninvasive assessment of liver fibrosis. Assuming the patient undergoes all 4 tests below, which of the following would suggest increased risk of having advanced liver fibrosis?

1. NAFLD Fibrosis score (NFS) of -2.5
2. FIB-4 index of -1.95
3. VCTE (Fibroscan) liver stiffness score of 5 kPa
4. MR Elastography liver stiffness score of 12 kPa
Serum markers of liver fibrosis in NAFLD have high NPV but low PPV

<table>
<thead>
<tr>
<th>Test</th>
<th>Compo-nents</th>
<th>AUROC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Cutoff</th>
<th>Fibrosis stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD Fibrosis Score (NFS)</td>
<td>Age, IFG/DM, BMI, Plt, AST/ALT</td>
<td>.81</td>
<td>51</td>
<td>96</td>
<td>-1.45 (low) 0.67 (high)</td>
<td>F3/4</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, AST, Plt, ALT</td>
<td>.88</td>
<td>26-74</td>
<td>71-98</td>
<td>-1.92 (low) 3.25 (high)</td>
<td>F3/4</td>
</tr>
<tr>
<td>APRI</td>
<td>AST/Plt</td>
<td>.67-.94</td>
<td>30</td>
<td>93</td>
<td>.45 (low) 1.5 (high)</td>
<td>F2-4</td>
</tr>
<tr>
<td>Fibrosure</td>
<td>Alpha2 macroglobulin, haptoglobin, GGT, Total bili, apoliprotein</td>
<td>.81-.92</td>
<td>15-77</td>
<td>77-90</td>
<td>.3 (low) .7 (high)</td>
<td>F2-4</td>
</tr>
<tr>
<td>BARD</td>
<td>BMI, AST/ALT ratio, DM</td>
<td>.8</td>
<td>86.8</td>
<td>32.5</td>
<td>2</td>
<td>F3/4</td>
</tr>
</tbody>
</table>

Kawala et al 2016 Dig Sci
A variety of new imaging technologies can noninvasively assess NAFLD fibrosis stage

- **VCTE- Fibroscan**
- **Shear Wave Ultrasonography**
- **MR Elastography**

Image sources: Echosens; GE Healthcare; Venkatesh et al 2013 J Magn Reson Imaging
Liver fat and fibrosis can be measured with CAP and VCTE (vibration-controlled transient elastography).

M probe: 25-65 mm depth
XL probe: 35-75 mm depth

VCTE score of <5 kPa suggests normal liver stiffness/no fibrosis; >12 suggests cirrhosis (cutoffs not well defined)
You recommend a liver biopsy based on VCTE of 10 kPa and she returns to discuss the result.

The pathologist’s report stages that the patient has 70% mixed macro- and microvesicular steatosis, foci of inflammation, Mallory hyaline, balloon degeneration, and bridging fibrosis (Metavir F3). Which of the findings on the biopsy should concern you the most?

1. The high degree of steatosis
2. The presence of Mallory hyaline
3. The high number of inflammatory foci
4. Balloon degeneration
5. Bridging fibrosis
Liver fibrosis is the feature most predictive of liver-related outcomes
Steatofibrosis predicts liver-related mortality just as well as steatohepatitis (NAS score)

Younossi, Hepat Comm, 2017

Steatofibrosis has much less inter-observer variability but similar association with liver-related mortality as NASH

Younossi, Hepat Comm, 2017
Liver fibrosis stage predicts liver-related mortality

Dulai, Hepatology, 2017
The patient wishes to avoid using a new medication at this time

You recommend weight loss as an option for management of NASH. Which of the following is most accurate about weight loss and NASH resolution?

1. At least 5% weight loss from baseline is needed to improve NASH
2. Exercise without associated weight loss can improve NASH and fibrosis
3. Only weight loss surgery but not lifestyle interventions can improve NASH
4. A minimum of 12-15% weight loss from baseline is required for improvement in NASH
NAFLD/NASH management should be based on disease stage

Rinella and Sanyal, Nat Rev Gastroenterol Hep, 2016
Weight loss is associated with improved liver histology in NASH
There is limited data on optimal dietary advice for patients with NAFLD

- The best diet to treat NAFLD is unknown (high protein diet?)
- >5% weight loss improves steatosis
- >7-9% weight loss improves histology in NASH
- Avoid saturated fats, sugary drinks, simple carbohydrates (fructose)
- A Mediterranean diet (monounsaturated fatty acids-rich) improves hepatic steatosis and insulin sensitivity
- Coffee consumption is associated with reduced risk of fibrosis in NASH patients

250 min/week of moderate exercise with weight loss may be optimal for improvement of NAFLD

Oh, 2015, Hepatology
Bariatric surgery can improve NASH in severely obese patients

82 patients at 1 year after surgery

Premature to consider weight loss surgery solely for NASH but can be considered if otherwise indicated (caution if cirrhosis/portal hypertension)

Lassailly, 2015, Gastroenterology
3 months after initial evaluation, the patient calls you about her dyslipidemia

The patient has elevated LDL, high triglyceride and low HDL and you consider starting a statin. LFTs show ALT 55, AST 48, other tests normal. What should you recommend at this time?

1. Defer starting a statin and repeat labs in 3 months
2. Start a statin now without additional testing
3. Start a statin but prefer pravastatin rather then atorvastatin
4. Use a non-statin cholesterol lowering drug
5. Avoid any medication due to potential hepatotoxicity in the setting of NASH, use lifestyle modification alone
Statins are safe and should not be withheld if indicated in NAFLD

AASLD 2017 NAFLD Guidance

1. NAFLD patients are at high risk for CVS morbidity and mortality
2. Aggressive CVD risk modification should be considered for all NAFLD patients
3. NAFLD/NASH patient are not at high risk from statins and they can be used for dyslipidemia
4. Avoid in decompensated cirrhosis
She returns in 6 months and has lost 3% weight from baseline

She has changed her diet and started walking but her weight has plateaued after initial weight loss. She wants to discuss pharmacotherapy. What should you recommend?

1. Due to her impaired fasting glucose, metformin is an excellent choice for NASH resolution
2. Off-label use of ursodeoxycholic acid is a safe and effective option
3. Omega-3 fatty acids can be used to improve steatosis
4. Off-label use of pioglitazone is a reasonable choice as she will likely lose ~4 kg as an off-target effect
5. None of the above
Pharmacotherapy for biopsy-proven NASH

• **Not recommended**
  - Ursodiol
  - Omega 3 fatty acid
  - Metformin
  - Off label Obeticholic acid

• **Treatments to consider**
  - Vitamin E (rrr alpha-tocopherol) 800 int units/daily in non-DM patients with NASH
  - Pioglitazone in patients with or without DM with biopsy-proven NASH (causes weight gain)
  - Consider clinical trial
There are over 200 ongoing clinical studies on NAFLD around the world.

Source: Clinicaltrials.gov, October 2016
Current therapies in development for NASH can be classified into four broad categories

1. Fat deposition and metabolic stress
   - Phase 3: Obeticholic acid (FXR agonist)
   - Phase 3: Elafibranor (PPAR α/δ agonist)

2. Inflammation, cell injury, oxidative stress
   - Phase 3: Selonsertib (ASK-1 inhibitor)

3. Fibrosis

4. Gut-liver axis
   - Phase 2: Veloxibat (Ileal ASBT inhibitor)
A year later, the patient’s sister presents to you to establish care

Her sister has a BMI of 34, T2DM, and a CT scan for suspected kidney stones shows fatty liver and splenomegaly. LFTs are normal, platelet count is 145,000. Which of the following is the most appropriate next step?

1. Recommend 5-10% weight loss and refer to a dietician
2. Start vitamin E 800 units daily and repeat CT in 6 months for resolution of NAFLD
3. Start metformin and a GLP-1 agonist for treatment of concurrent T2DM and NAFLD and monitor LFTs
4. Refer to a gastroenterologist ASAP
NASH may be associated with portal hypertension in the absence of cirrhosis

Mendes, 2012, Clin Gastroenterol Hepatol
NASH-related cirrhosis is associated with increased risk of hepatocellular carcinoma

- Annual cumulative incidence of HCC (3.2 yrs median follow up)
  - HCV-cirrhosis: 4%
  - NASH-cirrhosis: 2.6%

Ascha, 2010, Hepatology
Patients with NASH-cirrhosis and diabetes should continue metformin after cirrhosis diagnosis

Zhang, 2014, Hepatology
Outcomes after liver transplant for decompensated NASH cirrhosis are comparable to other etiologies.
Take home points

1. Rule out other etiologies of chronic liver disease and alcohol use while working up NAFLD
2. Consider noninvasive assessment of liver fibrosis to avoid need for liver biopsy in low risk patients
3. Liver biopsy recommended to confirm NASH with fibrosis before starting pharmacotherapy
4. Lifestyle modification is recommended for all stages of NAFLD, role of weight loss surgery is evolving
5. Consider pharmacotherapy (or clinical trial) for F2 or higher fibrosis
6. Patients with NASH-cirrhosis should be monitored for portal hypertension and HCC