Update in Non-Alcoholic Liver Disease in Diabetes

Jennifer Green, MD
Professor of Medicine
Duke University Medical Center
Division of Endocrinology, Metabolism and Nutrition

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NAFLD: Scope of the Problem

- Non-Alcoholic Fatty Liver Disease (NAFLD) in General Population
  - Global prevalence (by imaging) estimated to be 25.2%
  - Highest prevalence in Middle East (31.8%) and South America (30.5%)
  - Lowest prevalence in Africa (13.5%)
  - Prevalence of Non-Alcoholic Steato-Hepatitis (NASH) between 1.5-6.5%

- Common Conditions Associated with NAFLD
  - Obesity
  - T2DM
  - Dyslipidemia
  - Polycystic ovary syndrome

Economic Burden of NASH + T2DM in US Patients

- Estimated prevalence of NAFLD in DM is >70% (26% NASH)
  - >18 million people affected by both conditions

- Person-year cost higher with NASH ($2275 vs $95 with NAFLD)

- Costs of care for NASH + DM = $642 billion (25% specifically liver care)

- Projections over the next 20 years:
  - NASH + DM responsible for 64,900 liver transplants (29% of all txp)
  - 812,000 liver-related deaths
  - 1.37 million cardiovascular deaths
  - 1.27 million cases decompensated cirrhosis person-years
  - 479,000 HCC person-years
**Causes of NAFLD**

- **Lifestyle-dependent**
  - Overnutrition
  - Increased intake glucose, fructose, saturated fat
  - Gut dysbiosis due to unhealthy diet
  - Inactivity
- **Lifestyle-independent**
  - Ageing
  - Genetics

Stefan et al, Lancet diab+endo, April 2019

**Pathophysiology of NASH**

Schwabe RF, Gastroenterology 2012;142:711-725
T2DM and NAFLD

- Patients with T2DM more susceptible to severe NAFLD (fibrosis, cirrhosis)
- Higher progression to hepatocellular carcinoma
- Coexistence of disease conveys increased cardiovascular risk
  - Hepatic resistance to insulin-mediated suppression of VLDL secretion
  - Hypertriglyceridemia, low HDL cholesterol, small dense LDL particles
  - Hyperinsulinemia
  - Difficult to control hyperglycemia
- Increased risk of microvascular complications
  - Nephropathy, retinopathy
- Even moderate to severe fibrosis associated with higher mortality

Prevalence of NAFLD and Advanced Fibrosis in T2DM

A Prevalence of NAFLD using different diagnostic tools

B Overall prevalence of advanced fibrosis

Fernando Bril, and Kenneth Cusi Dia Care 2017;40:419-430
Diagnosis of NAFLD and NASH

- **Plasma alanine aminotransferase concentration** (ALT) has low sensitivity
- **Liver ultrasound** better than ALT, but limited ability to detect mild steatosis
- Various **algorithms and scores** based upon clinical variables
  - Most await validation/rigorous testing
  - Many patients fall into a “gray zone” intermediate risk category

Non-Invasive Estimation of Fibrosis

<table>
<thead>
<tr>
<th>Parameters and biomarkers</th>
<th>Cutoffs for advanced fibrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive biomarker detection methods</strong></td>
<td></td>
</tr>
<tr>
<td>NAFLD fibrosis</td>
<td>Age, BMI, IFG and diabetes, AST-to-ALT ratio, platelets, and albumin</td>
</tr>
<tr>
<td>FIB-4 index</td>
<td>Age, AST, ALT, and platelet</td>
</tr>
<tr>
<td>Enhanced liver fibrosis test</td>
<td>Age, hyaluronic acid, aminoterminal propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1</td>
</tr>
<tr>
<td>FibroTest</td>
<td>Total bilirubin, γ-glutamyltransferase, G2 macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and sex</td>
</tr>
<tr>
<td><strong>Non-invasive imaging</strong></td>
<td></td>
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<tr>
<td>VCTE</td>
<td>Ultrasound-based measurement of low-frequency (50 Hz) elastic shear wave velocity</td>
</tr>
<tr>
<td>MRE</td>
<td>MRI-based imaging of low-frequency mechanical waves</td>
</tr>
</tbody>
</table>

*Some indices have two cutoffs (to maximise sensitivity or specificity), which create gray zones of indeterminate values. For example, for the NAFLD fibrosis score, when applying the low cutoff score (1.455) advanced fibrosis could be excluded with high accuracy (negative predictive value of 93% in the estimation groups, and 88% in the validation groups). By applying the high cutoff score (0.676), the presence of advanced fibrosis could be diagnosed with high accuracy: NAFLD-non-alcoholic fatty liver disease. IFG=impaired fasting glucose. AST=aspartate aminotransferase. ALT-alanine aminotransferase. FIB-4=fibrosis-4. VCTE=vibration-controlled transient elastography. MRE=magnetic resonance elastography.
Performance of Non-Invasive Models

Non-invasive Diagnosis of Definite NASH

Non-invasive Diagnosis of Advanced Fibrosis

Diagnosis of NAFLD and NASH

- **Novel techniques** appear more accurate for diagnosis
  - Controlled attenuation parameter, MR and MRS based imaging for NAFLD
  - Fibroscan or MR elastography to determine degree of fibrosis
  - Cost, availability issues

- **Liver biopsy is the gold standard** test for diagnosis of NASH
  - r/o other diseases; distinguish isolated steatosis from NASH
  - To determine degree of fibrosis
  - Costly, inconvenient, risk of complications

MRS = magnetic resonance spectroscopy
**Diagnosis of NAFLD and NASH in Patients with Prediabetes or T2DM**

- **Patient with prediabetes or T2DM**
  - ALT or US abnormal
  - ALT & US normal

- **Assessment of fibrosis**
  - MRI elastography, or
  - Transient elastography, or
  - Fibrosis biomarker panels

- **Risk stratification**
  - High risk of fibrosis
  - Intermediate fibrosis risk
  - Low risk of fibrosis

- **Liver biopsy**
  - Absence of NASH
  - Periodic evaluation; standard care

- **Definitive NASH**
  - Lifestyle plus pharmacological treatment

- **Treatment of NASH**

  **Goals of treatment:**
  - Decreased disease activity
  - Delayed progression of fibrosis
  - Reducing cardiovascular risk

  **Aspects of treatment:**
  - Lifestyle modification
  - Pharmacologic treatment
  - Management hyperglycemia
  - Management dyslipidemia
  - Control of other CV risk factors

*A1c ≥ 8.5%
*TG ≥ 250 mg/dL

Fernando Bril, and Kenneth Cusi Dia Care 2017;40:419-430

Jennifer Green, MD
Non-Alcoholic Liver Disease in Diabetes
Pathogenesis and Potential Treatment Targets in NAFLD

- **Lipotoxicity:** Drugs which suppress lipogenesis or increase hepatic lipid export (aramchol, selective inhibitors of acetyl-coenzyme A-carboxylase, PPAR agonists)
- **Insulin Resistance:** PPAR agonists, GLP-1RA, SGLT2i, FGF 19/21 analogues
- **Oxidative Stress:** Vitamin E, SGLT2i
- **Inflammation/Apoptosis:** ASK1, CCR 2/5
- **Fibrosis:** Galectin-3 inhibitors
- **Bile Acid Recirculation:** Inhibitors of bile acid transporter (Sevelamer)
- **Farnesoid X Receptor Agonists:** decrease bile acid synthesis, hepatic lipo- and gluconeogenesis, increase insulin sensitivity
- **Gut Microbiota:** antibiotics, probiotics, microbial transfer

**Treatment effect vs. placebo for different histological outcomes for pharmacological agents assessed in randomized controlled trials reporting resolution of NASH as an outcome**

*Implies statistical significance*
Interventions for the Treatment of NAFLD

<table>
<thead>
<tr>
<th>Cardiometabolic effects</th>
<th>Hepatic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance Major cardiometabolic effects</td>
<td>Steatosis NAFLD Steatosis NAS Fibrosis</td>
</tr>
<tr>
<td>Lifestyle modification Moderate decrease Weight loss, and mild decrease in dyslipidemia</td>
<td>Yes Moderate decrease Moderate decrease Small decrease or no effect</td>
</tr>
<tr>
<td>and blood pressure</td>
<td></td>
</tr>
<tr>
<td>Bariatric surgery Substantial decrease Weight loss, and mild decrease in dyslipidemia</td>
<td>Yes Substantial decrease Substantial decrease Substantial decrease Small decrease</td>
</tr>
<tr>
<td>and blood pressure</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones Substantial decrease Mild decrease in dyslipidemia and blood pressure</td>
<td>Yes Substantial decrease Substantial decrease Small decrease or no effect</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 receptor agonists Small decrease Weight loss</td>
<td>Yes Moderate decrease Moderate decrease No effect</td>
</tr>
<tr>
<td>Exenatide Small decrease Weight loss</td>
<td>No Moderate decrease NA NA</td>
</tr>
<tr>
<td>Dipeptidyl peptide-4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Vildagliptin No effect</td>
<td>No No effect</td>
</tr>
<tr>
<td>Sodium-glucose co-transporter-2 inhibitors</td>
<td>NA NA</td>
</tr>
<tr>
<td>Canagliflozin Small decrease Weight loss and small decrease in blood pressure</td>
<td>Yes Small decrease NA NA</td>
</tr>
<tr>
<td>Empagliflozin Small decrease Weight loss and small decrease in blood pressure</td>
<td>Yes NA NA</td>
</tr>
<tr>
<td>Dapagliflozin Small decrease Weight loss and small decrease in blood pressure</td>
<td>Unknown No effect</td>
</tr>
<tr>
<td>Lizagliflozin* NA</td>
<td>Unknown Small decrease NA</td>
</tr>
<tr>
<td>Spagliflozin* NA</td>
<td>Unknown Small decrease NA</td>
</tr>
<tr>
<td>Antioxidants</td>
<td></td>
</tr>
<tr>
<td>Vitamin E No effect</td>
<td>Small decrease in oxidative stress and potential small decrease in inflammation</td>
</tr>
<tr>
<td>Phosphatidylcholine inhibitors</td>
<td>No (potentially harmful) Moderate decrease Moderate decrease? No effect</td>
</tr>
<tr>
<td>Pentoxifylline No effect</td>
<td></td>
</tr>
</tbody>
</table>

Data are from randomized controlled trials only. NAFLD = non-alcoholic steatohepatitis. NA = no data available. *Randomized open-label trials. #Significant effect on NAFLD in patients with type 2 diabetes.

SGLT2i for the Treatment of NAFLD

### Table 1—Effect of SGLT2i in NAFLD

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Agent</th>
<th>n</th>
<th>Duration (weeks)</th>
<th>Comparator</th>
<th>Body weight*</th>
<th>ALT</th>
<th>Liver fat*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective open-label studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ito et al., 2017 (42)</td>
<td>Ipragliflozin</td>
<td>66</td>
<td>24</td>
<td>Pioglitazone</td>
<td>↓ 3.7%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ohta et al., 2017 (43)</td>
<td>Ipragliflozin</td>
<td>20</td>
<td>24</td>
<td>Standard care</td>
<td>↓ 2.5%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Shibuya et al., 2018 (44)</td>
<td>Luseogliflozin</td>
<td>32</td>
<td>24</td>
<td>Standard care</td>
<td>↓ 3.2%</td>
<td>Unchanged</td>
<td>↓</td>
</tr>
<tr>
<td>Kuchay et al., 2018 (45)</td>
<td>Empagliflozin</td>
<td>50</td>
<td>20</td>
<td>Standard care</td>
<td>↓ 1.1%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Shimizu et al., 2019 (46)</td>
<td>Dapagliflozin</td>
<td>57</td>
<td>24</td>
<td>Standard care</td>
<td>↓ 3.1%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Inoue et al., 2019 (47)</td>
<td>Canagliflozin</td>
<td>20</td>
<td>52</td>
<td>Standard care</td>
<td>↓ 3.4%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolinder et al., 2012 (48)</td>
<td>Dapagliflozin</td>
<td>67</td>
<td>24</td>
<td>Placebo</td>
<td>↓ 2.2%</td>
<td>—</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Eriksson et al., 2018 (49)</td>
<td>Dapagliflozin</td>
<td>84</td>
<td>12</td>
<td>Placebo</td>
<td>↓ 2.2%</td>
<td>↓</td>
<td>↓ 10%</td>
</tr>
<tr>
<td>Cosi et al., 2019 (50)</td>
<td>Canagliflozin</td>
<td>56</td>
<td>24</td>
<td>Placebo</td>
<td>↓ 3.4%</td>
<td>Unchanged</td>
<td>↓ 18%</td>
</tr>
<tr>
<td>Latva-Raska et al., 2019 (51)</td>
<td>Dapagliflozin</td>
<td>32</td>
<td>8</td>
<td>Placebo</td>
<td>↓ 2.1%</td>
<td>Unchanged</td>
<td>↓ 13%</td>
</tr>
<tr>
<td>Kahl et al., 2019 (52)</td>
<td>Empagliflozin</td>
<td>84</td>
<td>24</td>
<td>Placebo</td>
<td>↓ 2.4%</td>
<td>Unchanged</td>
<td>↓ 22%</td>
</tr>
</tbody>
</table>

Arrows indicate statistically significant changes vs. comparator. *Comparison-corrected (open-label) or placebo-corrected relative treatment difference in weight and liver fat measured with MRI-based imaging techniques. †Liver fat measured as liver-to-spleen attenuation ratio on computed tomography. In Ito et al. (42) the decrease in liver fat was similar to pioglitazone (comparator). ‡Significant improvement in liver fat by controlled attenuation parameter (CAP; Fibroscan). §Not significant compared with placebo.
Management of Patients with Prediabetes or T2DM and Definite NASH

Patient with prediabetes or T2DM and definite NASH

Treatment of NASH
- Pharmacological treatment: Pioglitazone as first-line therapy
- Lifestyle intervention: Weight reduction of 8-10%
- Second-line therapies

Control of other CV risk factors
- Glucose control: Metformin as first-line therapy
- Blood pressure control: ARB or ACEI as first-line therapy
- Lipid-lowering therapy: Statins as first-line therapy
- Elevated A1c
- Elevated BP
- Elevated TG and low HDL
- Add fibrates to statins?

Statin Treatment in NAFLD and NASH

Long-term statin treatment and liver toxicity
1. As per the national lipid association (NLA), the risk for serious liver injury from statins is quite rare.
2. LFT monitoring in asymptomatic individuals is not recommended.

Statin use for the treatment of dyslipidemia in patients with nonalcoholic fatty liver disease
1. Patients with NAFLD are at high risk of cardiovascular morbidity and mortality.
2. Treatment of dyslipidemia plays a critical role in the overall management of NAFLD.
3. Patients with NAFLD and dyslipidemia are not at increased risk of statin hepatotoxicity.
4. Statins reduce CVD morbidity and mortality in patients with NAFLD/NASH by two-fold times compared with untreated patients not on statins.

Statin use for the treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis
1. Preliminary studies have shown that statins may possibly improve hepatic histology in patients with underlying NAFLD; however, no convincing histological data are available.
2. At present, statins are not recommended for treatment of NASH.

LFT, liver function test; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; CVD, cardiovascular disease.
Patient with Diabetes and Elevated ALT

A 60 year old female is referred for evaluation of “fatty liver and elevated liver enzymes.”

She has had mild aminotransferase elevation (ALT in the 50s U/L [> 0.835 μkat/L]) for many years, but her recent labs show persistent elevation of aminotransferases (despite a 2-month statin holiday):

- AST 80 (1.34 μkat/L)
- ALT 92 (1.54 μkat/L)
- Albumin 4.0 (40 g/L)
- Bilirubin and alkaline phosphatase are normal.
- Platelets 210
Patient with Diabetes and Elevated ALT

Other data:
- HbA1c 6.2% (44 mmol/mol)
- Ultrasound 3 years ago showed fatty liver.

- Medications:
  - amlodipine, atorvastatin, enalapril, metformin, omeprazole
- PMH:
  - hypertension, type 2 diabetes, elevated LDL cholesterol, GERD, anxiety
  - She does not like alcohol.
  - BMI 31.0
  - Waist circumference 114 cm

What Other Tests Could Be Considered?

Ultrasound shows:
- “increased echogenicity of the liver parenchyma, likely consistent with hepatic steatosis”
- No other hepatic abnormalities.
- No splenomegaly.

Labs:
- HCV & HBV: negative
- ASMA, ANA: normal
- A1AT, iron profile: normal
Patient with Diabetes and Elevated ALT

- Other causes of liver enzyme elevation are ruled out.
- Her ultrasound suggests fatty liver.

Is it enough to conclude that her aminotransferase elevation is relatively mild and that it is due to NAFLD?

- Do we need to ask whether or not she has NASH? And how would we evaluate for NASH?
How Would You Evaluate for NASH?

While liver biopsy is the gold standard, are there any steps we can take before liver biopsy?

Patient with Diabetes and Elevated ALT

Noninvasive scoring methods

- **APRI**  [https://www.mdcalc.com/ast-platelet-ratio-index-apri](https://www.mdcalc.com/ast-platelet-ratio-index-apri)
- **FIB-4**  [https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis](https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis)
- **NAFLD FIBROSIS SCORE (NFS)**  [https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score](https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score)

These scores can be calculated without special serologic testing.

Data used:
- platelets, ast, alt, albumin
- age, BMI, presence of IFG or diabetes
Patient with Diabetes and Elevated ALT

**APRI**

\[
\text{APRI} = \frac{\text{AST Level (IU/L)}}{\text{Platelet Count (10^9/L)}} \times 100
\]

**Interpretation:**
In a meta-analysis of 40 studies, investigators concluded that an APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. In addition, they concluded that APRI score greater than 0.7 had a sensitivity of 79% and specificity of 73% for predicting significant hepatic fibrosis. For detection of cirrhosis, using an APRI cutoff score of 2.0 was more specific (91%) but less sensitive (44%). The lower the APRI score (less than 0.5), the greater the negative predictive value (and ability to rule out cirrhosis) and the higher the value (greater than 1.5) the greater the positive predictive value (and ability to rule in cirrhosis); midrange values are less helpful. The APRI alone is likely not sufficiently sensitive to rule out significant disease. Some evidence suggests that the use of multiple indices in combination (such as APRI plus FibroTest) or an algorithmic approach may result in higher diagnostic accuracy than using APRI alone.

**Patient with Diabetes and Elevated ALT**

**FIB-4**

\[
\text{FIB-4} = \frac{\text{Age (years)}}{\text{AST Level (IU/L)}} \times \frac{\text{Platelet Count (10^9/L)}}{\sqrt{\text{ALT (IU/L)}}}
\]

**Interpretation:**
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

APRI > 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis.

FIB-4 > 3.25 would have a 97% specificity and positive predictive value of 65% for advanced fibrosis.
NAFLD FIBROSIS SCORE (NFS)

Fibrosis Staging

<table>
<thead>
<tr>
<th>Score</th>
<th>Suggested fibrosis stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>0.95</td>
</tr>
<tr>
<td>FIB-4</td>
<td>2.4</td>
</tr>
<tr>
<td>NFS</td>
<td>0.08</td>
</tr>
</tbody>
</table>

NFS score between 
-1.455 – 0.675 =
indeterminate score

Patient with Diabetes and Elevated ALT

Non-invasive calculators have limitations;
However, they are inexpensive and easy to calculate with platelets, ast, alt, and albumin (and age, bmi, & presence of impaired fasting glucose or diabetes for NFS).

Patient with Diabetes and Elevated ALT

Imaging-based non-invasive methods

- VCTE (Fibroscan)
- MR elastography

MR elastography was not available to the patient, so she had a Fibroscan.

Fibroscan (VCTE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>IQR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (m/s)</td>
<td>2.31</td>
<td>0.16</td>
</tr>
<tr>
<td>E (kPa)</td>
<td>16</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Liver stiffness > 9.9 kilopascals suggests advanced fibrosis (95% sensitivity, 77% specificity)

(AASLD NAFLD Practice Guidance, Hepatol 2018, p336)
Based on These Non-invasive Tests, Would You Recommend Liver Biopsy?

<table>
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<th>Score</th>
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<td>FIB-4</td>
<td>2.4</td>
</tr>
<tr>
<td>NFS</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibroscan</td>
<td>16.0 kpa</td>
</tr>
</tbody>
</table>

If a Biopsy Shows NASH with Significant Fibrosis, How Would that Change the Treatment Plan?

- Weight loss should already be recommended.
- She should optimize control of diabetes and address risks for cardiovascular disease.
- Consider medical treatments directed at NASH
- May alter choice of antihyperglycemic agents
Patient with Diabetes and Elevated ALT

Given her risk factors for NASH (DM2, metabolic syndrome, elevated non-invasive scores), she proceeds with liver biopsy.

LIVER BIOPSY (N): STEATOHEPATITIS, NONALCOHOLIC BY HISTORY, WITH BRIDGING FIBROSIS

MICROSCOPIC DESCRIPTION:
The sections obtained after processing show three needle cores with aggregate length of 35 mm, embedded in two blocks. More than eleven portal tracts are present. The biopsy shows steatosis, with lobular and portal inflammation, as well as hepatocellular ballooning and a number of Mallory bodies, indicating an active steatohepatitis. The trichrome stain shows centrilobular pericellular fibrosis and periportal fibrosis with extensive bridging fibrosis but not cirrhosis.

SPECIAL STAINS:
The Masson trichrome stain shows bridging fibrosis. Control sections are appropriately positive.

Patient with Diabetes and Elevated ALT, Diagnosed with NASH with Bridging Fibrosis

In addition to the previous recommendations (weight loss, diabetes control, address CV risks),
- She should be followed closely for progressive liver disease.
- She could be considered for HCC screening and surveillance.
- If she cannot achieve sustained weight loss, bariatric surgery could be considered
- Pioglitazone a reasonable consideration
- Other antihyperglycemic therapies being studied in NAFLD/NASH, but not specifically recommended at this time