Nonalcoholic Fatty Liver Disease (NAFLD): Screening, Current Management and Treatments on the Horizon

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Texas Liver Institute
Overview

• Describe the burden, disease spectrum and natural history of NAFLD.

• Discuss management strategies for patients with NAFLD:
  • Noninvasive diagnosis of disease severity
  • Novel therapeutic agents expected to be available in the near future
Case Presentation

Tony

- 60 y.o. M with DM2, BMI of 39 kg/m² and MetS.
- Presents with persistently elevated LFTs.
- ALT 66 U/L (10-40 U/L)
- AST 76 U/L (10-40 U/L)
- Albumin 3.5 g/dL (3.5-4.5 g/dL)
- Platelet count 170 k/uL (150-400 k/uL)

Weakness
Epidemiology and Natural History of NAFLD
NAFLD is the Hepatic Manifestation of Obesity/IR

Metabolic Syndrome
- Insulin Resistance
- Dyslipidemia
- Hypertension

NAFLD
NAFLD Prevalence

Adults

• Overall: ~ 25%
• Obese: ~ 50%
• Severely Obese: ~ 85%
• DM2: ~ 65-75%
The NAFLD Spectrum

NAFL → Early NASH → Fibrotic (F2-F3) → NASH Cirrhosis

NAFLD Activity Score

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Steatosis (0-3)</td>
<td></td>
</tr>
<tr>
<td>5-33%</td>
<td>1</td>
</tr>
<tr>
<td>34-65%</td>
<td>2</td>
</tr>
<tr>
<td>≥66%</td>
<td>3</td>
</tr>
<tr>
<td>Inflammation (0-3)</td>
<td></td>
</tr>
<tr>
<td>&lt;2 under 20x</td>
<td>1</td>
</tr>
<tr>
<td>2-4 under 20x</td>
<td>2</td>
</tr>
<tr>
<td>&gt;4 under 20x</td>
<td>3</td>
</tr>
<tr>
<td>Ballooning (0-2)</td>
<td></td>
</tr>
<tr>
<td>Few</td>
<td>1</td>
</tr>
<tr>
<td>Many</td>
<td>2</td>
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</tbody>
</table>

Steatosis, Neutrophils, Mallory hyaline, Ballooned hepatocyte
Fibrosis Stage is the Most Important Prognostic Factor in Predicting Liver-related Outcomes

Relative to NAS 1-2:
- NAS 3-4
- NAS 5-8

Relative to F0:
- F1
- F2
- F3
- F4

Hazard Ratios and 95% CIs of Outcome Mortality/Liver Transplantation

NASH is the Most Common Indication for Listing and OLT in Women in the U.S.
Determining the Presence and Severity of NAFLD
Current Diagnosis of NAFLD: ALT and Ultrasonography

ALT can be normal in patients with NAFLD

ALT/US cannot diagnose NASH or stage the severity of fibrosis in patients with NAFLD
Noninvasive Diagnosis of Fibrosis

- **Simple**
  - AST/ALT ratio
  - APRI
  - FIB-4
  - NFS

- **Complex**
  - FibroSURE
  - ELF
  - HA

- **Imaging**
  - VCTE
  - MRE
  - ARFI

- **Elastography**
Fibrosis-4 (FIB-4) Calculator

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

**Interpretation:**
- < 1.4: absence of significant fibrosis
- 1.4-2.66: Indeterminate
- > 2.67: presence of advanced fibrosis

**Score**
- 3.30

**Original score**
- 4.040

< 1.455: predictor of absence of significant fibrosis (F0-F2 fibrosis)
\leq -1.455 to \leq 0.675: indeterminate score
> 0.675: predictor of presence of significant fibrosis (F3-F4 fibrosis)
**Fibrosure™**

- **6 Serum Markers**
  - A2-macroglobulin
  - Haptoglobin
  - Apolipoprotein A1
  - Total bilirubin
  - GGT
  - ALT

### Metavir scale

<table>
<thead>
<tr>
<th>Fibrosis Stage (FibroTest)</th>
<th>Activity Grade (ActiTest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 - No fibrosis</td>
<td>A0 - No activity</td>
</tr>
<tr>
<td>F0 - F1</td>
<td>A0 - A1</td>
</tr>
<tr>
<td>F1 - Portal fibrosis</td>
<td>A1 - Minimal activity</td>
</tr>
<tr>
<td>F1 - F2</td>
<td>A1 - A2</td>
</tr>
<tr>
<td>F2 - Bridging fibrosis with few septa</td>
<td>A2 - Moderate activity</td>
</tr>
<tr>
<td>F3 - Bridging fibrosis with many septa</td>
<td>A2 - A3</td>
</tr>
<tr>
<td>F3 - F4</td>
<td>A3 - Severe activity</td>
</tr>
<tr>
<td>F4 - Cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

- F0: 0.00 - 0.21
- F1: 0.21 - 0.27
- F2: 0.27 - 0.31
- F3: 0.31 - 0.48
- F4: 0.48 - 0.58
- Cirrhosis: 0.58 - 0.72
- Activity: 0.72 - 0.74
- Severe: 0.74 - 1.00
Shear Wave Movement

Controlled Frequency 50 Hz Shear Wave
Staging the Severity of Steatosis and Fibrosis in NAFLD: VCTE + CAP
VCTE + CAP: A Powerful Tool
<table>
<thead>
<tr>
<th>Transient Elastography (kPa)</th>
<th>MR Elastography (kPa)</th>
<th>ARFI (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
<td></td>
</tr>
<tr>
<td>- Can be performed in clinic with real-time results</td>
<td>- Increased failure rate with obesity</td>
<td>- Can be integrated into a conventional ultrasound</td>
</tr>
<tr>
<td>- Accurate in obese patients and examines the entire liver</td>
<td>- Expensive and time consuming</td>
<td></td>
</tr>
<tr>
<td>- Can be integrated into a conventional ultrasound</td>
<td>- Limited availability</td>
<td>- Increased failure rate with obesity</td>
</tr>
<tr>
<td>- Only a few published studies</td>
<td>- Cutoff values for advanced fibrosis vary significantly</td>
<td></td>
</tr>
<tr>
<td>- Cutoff values with XL probe need further validation</td>
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NAFLD Management: Current and Future
How Do I Manage My Patient with NAFLD Today

- Rule out other etiologies of elevated ALT or fatty infiltration of the liver
- Assess for co-morbidities (DM2, HTN, Dyslipidemia, OSA)
- Assess severity (NASH, advanced fibrosis)
- Treatment:
  - Lifestyle
  - Pharmacologic
## Laboratory Assessment for NAFLD

### Chronic Liver Disease Panel
- CBC + AUTO DIFF
- HEPATIC FUNCTION PNL
- GGT BLD
- BASIC METABOLIC PNL
- LIPID PANEL BASIC
- PROTHROMBIN TIME/PT
- HEP REMOTE PANEL BL
- HEP A AB TOTAL
- ANA BLOOD
- SMOOTH MUSCLE AB PNL SCR
- LKM AB
- ALPHA-1-ANTITRYPS BL
- IRON + TIBC
- FERRITIN BLD
- CERULOPLASMIN BLD
- CELIAC SCREEN WITH REFLEX
- CK CREATINE KINASE

### NASH Panel
- CBC + AUTO DIFF
- HEPATIC FUNCTION PNL
- GGT BLD
- BASIC METABOLIC PNL
- LIPID PANEL BASIC
- TSH BLD
- HGB A1C
- INSULIN ASSAY BLOOD
- GLUCOSE FASTING BLD
- C-REACTIVE ULTRA SEN
- LIPOPROTEIN (A)
- ALBUMIN RANDOM URINE
- VITAMIN D 25 HYDROXY
Assessment of the Severity of NAFLD

[Image of a machine with buttons labeled Age (years), BMI (kg/m²), IGF/diabetes, AST, ALT, Platelets (x10⁹/l), Albumin (g/l).]

[Text about the NAFLD fibrosis score calculator, including references and calculation input fields.]
Patient with DM2 or MetS

Screen for NAFLD with ALT and US

Determine Severity with NFS and FIB4

- NFS < -1.455 and FIB4 < 1.4
  - No advanced disease
  - Consider repeating every 2-3 years
  - Lifestyle modifications

- Indeterminate zone or discordant
  - FibroTest
    - Low
    - High

- NFS > 0.676 and FIB4 > 2.67
  - Advanced fibrosis
  - Refer to GI/Hepatology
Treatment: % Weight Loss Associated With Histological Improvement

Fibrosis (45%)

NASH Resolution (64%–90%)$^a$

Ballooning/Inflammation (41%–100%)$^a$

Steatosis (35%–100%)$^a$

- Weight Loss ≥10%$^{12}$
- Weight Loss ≥7%$^{12}$
- Weight Loss ≥5%$^{5,7,12}$
- Weight Loss ≥3%$^{5,7,12-13}$
Changing the Attitude Toward Healthy Lifestyle in Texas
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

- 247 patients with NASH and w/o DM
  - Pioglitazone: 30 mg/d
  - Vitamin E: 800 IU/d
  - Placebo

- Primary outcome: Improvement in histologic features of NASH
Resolution of NASH with Vitamin E and Pioglitazone Compared to Experimental Drugs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Vitamin E 800 IU/day</td>
<td>36</td>
</tr>
<tr>
<td>Pioglitazone 30 mg/day</td>
<td>21</td>
</tr>
</tbody>
</table>

- **Vitamin E**: Increased overall mortality/stroke/prostate cancer
- **Pioglitazone**: Increased risk of bladder cancer, osteoporosis/? HF

Sanyal A et al. *NEJM* 2010
The Race to Cure NASH: Six Medications in Phase III Controlled Trials

- Elafibranor
- Aramchol
- MGL-3196
- **Obeticholic acid (OCA):** FXR agonist (REGENERATE)
- **Cenicriviroc (CVC):** CCR2/CCR5 inhibitor (AURORA)
- **Selonsertib:** Apoptosis signal-regulating kinase (ASK1) inhibitor (STELLAR-3)

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Alkhouri et al. *Clinical Liver Disease.* 2018
NAFLD is the New Type 2 Diabetes!

TE with CAP is the New HbA1C
The NAFLD Spectrum

**NAFL**
- HbA1C 5.7-6.4
- Pre-Diabetes
- TE < 6 kPa
- CAP > 250 db/m
- Lifestyle Modifications

**Early NASH**
- HbA1C 6.5-8.5
- Controlled DM2
- TE 7-8 kPa
- CAP > 250 db/m
- Elafibranor
  - ACC inhibitor

**Fibrotic (F2-F3)**
- HbA1C > 8.5
- Uncontrolled DM2
- TE 9-14 kPa
- CAP > 250 db/m
- OCA, CVC, ASK1

**NASH Cirrhosis**
- Diabetes Complications
  - CKD,
  - Retinopathy,
  - CAD
- TE >15 kPa
- TE > 25 kPa
- Combination
  - HCC/EV Screening
How Do We Manage NAFLD at The Texas Liver Institute?

Tina

- 50 y.o. F with BMI of 42 kg/m² and MetS presents with elevated LFTs. ALT 66, AST 56, albumin 4.5, platelet count of 270.
  - CAP = 356, TE = 4.8 → Consistent with NAFL (= pre-diabetes)
  - **Lifestyle modifications: weight loss of 7-10% + exercise**
  - Follow up Fibroscan every 1-2 years.
How Do We Manage NAFLD at The Texas Liver Institute?

Tony

• 60 y.o. M with DM2, BMI of 39 kg/m2 and MetS presents with elevated LFTs. ALT 66, AST 76, albumin 3.5, platelet count of 170.
  • TE = 12.8 → Consistent with advanced fibrosis (F3-F4)
  • Refer to stage 3 fibrosis clinical trials: STELLAR3 (ASK1 inhibitor), REGENERATE (OCA), or AURORA (CVC)
  • Consider HCC screening with US every 6 months

Weakness
NAFLD is very common and a serious liver disease even among young adults.

Screening for NAFLD should be considered in patients with DM2 and MetS.

The severity of NAFLD-associated fibrosis can be determined with non-invasive methods.

NASH-specific therapies are coming soon and should change the attitude toward screening and treatment.
Q&A/Panel Discussion

Drs. Lawitz, Rodas & Alkhouri
15 Minute Break