MAFLD
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DISCLOSURE

• I disclose that I have no conflict of interest
Diagnosis of MAFLD

OUTLINE

• MAFLD Introduction
• MAFLD Vs NAFLD
• Diagnosis of MAFLD
• Case presentation
• Summary of treatment options
CASE

- Mr. X
- Age: 65 years
- Sex: Male
- Weight: 80 kg, Ht=170 cm; BMI= 27.7 kg/m²
- Comorbidity: Type 2 DM,
- Medications: Insulin, Metformine
History:

Fatigue, Abdominal swelling, jaundice, a single episode of hematemesis

Examination:

- Icteric Sclerae
- Moderate pallor
- Ascites ++
- Peripheral edema +
CASE

- Hgb=9gm/dl, Bil (T)=0.91, Sodium=136, paletlet=86, INR=2.03, Vitamin D=16, calcium=9.6, AST=55, ALT=33, ALb=3.3, ALP=284 (0-270), creatinine=0.88,
- HBsAg=Neg; HCVAb=Neg,
- MELDNa= 17

- Abdominal US: Cirrhosis, Ascites, splenomegaly (mild)
- EGD: Large Varices
- Further assessment of this patient?
NAFLD
Definition

- NAFLD: Hepatic steatosis - - - Steatohepatitis - - - Cirrhosis
  - Exclusion 2ry causes
- NASH: ≥5% hepatic steatosis with inflammation and hepatocyte injury (also known as hepatocyte ballooning), +/- liver fibrosis.
- NAFLD is a diagnosis of exclusion
MAFLD

Definition

• The presence of hepatic steatosis with at least one of the following:
  • Obesity
  • Type 2 DM
  • Metabolic disease

MAFLD is not a diagnosis of exclusion
MAFLD
Definition

Hepatic steatosis in adults

Overweight/obesity  Type 2 diabetes  Lean/normal weight

Presence of at least two of the following metabolic risk abnormalities:

1. Waist circumference $\geq 102$ cm in Caucasian men and $\geq 88$ cm in women (or $\geq 90$ in Asian men and $\geq 80$ in Asian women)
2. Blood pressure $\geq 130/85$ mmHg or hypertension drug treatment
3. Plasma triglycerides $\geq 150$ mg/dL ($\geq 1.70$ mol/L) or its drug treatment
4. Plasma HDL-cholesterol $< 40$ mg/dL ($< 1.0$ mmol/L) for men and $< 50$ mg/dL ($< 1.3$ mmol/L) for women or its drug treatment
5. Prediabetes
6. Homeostasis model assessment of insulin resistance (HOMA-IR) score $\geq 2.5$
7. Plasma high-sensitivity C-reactive protein level $> 2$ mg/L
THE CONTINUUM

- Insulin-resistant adipose tissue
- Compensated Steatosis
- SH “Decompensated steatosis”
- Fibrosis

Natural history and outcomes

- Steatosis + inflammation
- Steatohepatitis
- Early fibrosis
- Advanced fibrosis and cirrhosis

- Risk of HCC
- Risk of death or transplantation

Cardiovascular disease risk

Extrahepatic cancers (>GI tract) risk

J HEP, 2022
NAFLD
Secondary causes of steatosis

Excessive alcohol consumption
Hepatitis C (genotype 3)
Lipodystrophy
Acute weight loss
(bariatric surgery and starvation)
Malnutrition
Parenteral nutrition
Abetalipoproteinemia
Reye syndrome
Pregnancy associated
  HELLP syndrome
  Acute fatty liver of pregnancy

Medications
  corticosteroids, Mipomersen, Lomitapide, Amiodarone
  Methotrexate, Tamoxifen
  Valproate, ARV Medications

Other causes
  Autoimmune hepatitis
  A1AT deficiency
  Wilson syndrome ...
NAFLD

Lab evaluation: Secondary causes of steatosis

Hepatitis C
  HCV antibody with reflex testing HCV RNA
Additional tests to consider:
  Hepatitis B: HBsAg, HBsAb, and HBCAb
ANA
AMA
ASMA
Immunoglobulins
Ferritin
A1AT
From NAFLD to MAFLD

NAFLD
- No alcohol intake >20 grams/day
- No other causes of liver disease (e.g. viral, autoimmune, wilson’s, hemochromatosis, DILI)

MAFLD
Overweight/obesity OR Type 2 Diabetes OR at least two:
- Visceral obesity
- Arterial hypertension
- High triglycerides
- Low HDL
- Prediabetes
- HOMA.2.5
- H-S PCR > 2 mg/L
Distribution of severity of hepatic steatosis

CHB + MAFLD (n = 1,083)
- Mild: 62.0%
- Moderate: 13.7%
- Severe: 24.4%

CHB + NAFLD outside MAFLD criteria (n = 51)
- Mild: 35.3%
- Moderate: 13.7%
- Severe: 51.0%

$p < 0.001$
Which adults with NAFLD should be considered at “high risk” of clinically significant fibrosis (stages F2-F4) and at risk of cirrhosis?

- Persons with obesity and/or features of metabolic syndrome
- Prediabetes or T2D, and
- Those with hepatic steatosis on any imaging study and/or
- Persistently elevated plasma aminotransferase levels (over 6 months)

- High risk patients should be screened for NAFLD and advanced fibrosis
**Association of MAFLD and Extrahepatic Manifestations**

- Obesity
- Diabetes - Type 2, Type 1*
- Hypertryglyceridemia
- Metabolic syndrome
- CVD
- CKD
- Extrahepatic Malignancies (e.g. Colorectal cancer)
- PCOS

- Sleep Apnea
- Sarcopenia
- Osteoporosis
- Psoriasis
- Hypothyroidism
- Hypopituitarism

Should all persons with diabetes mellitus be screened for clinically significant fibrosis (stages F2-F4) associated with NAFLD?

- In persons with Type 2 DM
  - Liver enzymes
  - FIB-4
- In type 1 DM
  - Patients with risk factors such as obesity, features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.
### Guideline Recommendations: Who Is at Risk for NASH and Advanced Fibrosis?

<table>
<thead>
<tr>
<th>AASLD(^1)</th>
<th>EASL-EASD-EASO(^2)</th>
<th>ADA(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In type 2 diabetes, <strong>suspect NAFLD and NASH</strong> and determine patient’s risk of advanced fibrosis. Increasing number of metabolic diseases = <strong>increasing risk of progressive liver disease</strong>. “There should be a high index of suspicion for NAFLD and NASH in patients with T2DM,” but did not recommend systematic screening for NAFLD.</td>
<td><strong>NAFLD screening recommended</strong> in persons at high CVD risk, including type 2 diabetes or metabolic syndrome.</td>
<td>NASH and fibrosis <strong>screening recommended</strong> in persons with type 2 diabetes or prediabetes and elevated ALT or fatty liver.</td>
</tr>
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T2D as a Risk for Advanced Fibrosis (by Diagnostic Approach)

- Meta-analysis (N = 3229)

Why do we Assess Fibrosis?

Increase Fibrosis stage is associated with significant Mortality

Meta Analysis of 5 studies with 1,495 NAFLD patients and 17,452 patient years

Dulai et al. *Hepatology* 2017
Non-invasive scoring algorithms to assess fibrosis

**FIB-4 index**

\[
FIB-4 = \frac{\text{Age (yrs)} \times \text{AST (U/L)}}{\text{Plts (10}^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}
\]

**NAFLD fibrosis score**

\[
\text{NFS} = -1.675 + 0.037 \times \text{age [yrs]} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/DM (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT} - 0.013 \times \text{plts (10}^9/\text{L}) - 0.66 \times \text{albumin (g/dL)}
\]

<table>
<thead>
<tr>
<th>NAFLD Score</th>
<th>Correlated Fibrosis Severity</th>
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<tbody>
<tr>
<td>&lt; -1.455</td>
<td>F0-F2</td>
</tr>
<tr>
<td>-1.455 – 0.675</td>
<td>Indeterminant score</td>
</tr>
<tr>
<td>&gt; 0.675</td>
<td>F3-F4</td>
</tr>
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</table>
Role of Liver Enzymes

- ALT: considered liver specific markers
  - Used in both FIB-4; NFS with AST
- ALT is non-specific in NAFLD/NASH (Normal > 50% NASH; 80% NAFLD), can be elevated in NAFLD with out NASH
- The ratio of AST/ALT usually is less than 1 (unless in advanced cases)
- Abnormal ALT may warrant work up for NAFLD
- Alkaline phosphatase may be elevated up to twice the upper limit of normal;
  - γ-glutamyltransferase (GGT) also may be elevated.
Common Imaging Tests for Hepatic Fibrosis

Vibration-controlled transient elastography – *FibroScan*
- Can be point of care
- Most reliable in ruling out advanced hepatic fibrosis (great NPV)

MR elastography/MR spectroscopy/ liver multiscan
- Requires radiology referral
- Most accurate of the imaging modalities

2D shear wave elastography
- May require radiology referral but can be point of care with minimal training

These imaging tests measure liver stiffness, which is an indirect measure of hepatic fibrosis and not hepatic fat content
Example of a Proposed Sequence of Testing in NAFLD

- If NAFLD, rule out low risk with either:
  - **Serum biomarker/algorithm** (FIB-4, NFS, ELF) or
  - **Imaging** (VCTE, MRE, or shear wave elastography)
- If low risk not ruled out, use the other modality to confirm intermediate or high risk

- NAFLD
  - US, CT, MRI, VCTE
- NASH
  - Liver biopsy
- Advanced fibrosis
  - FIB4, APRI, proprietary panels
  - VCTE/ARFI
  - MR elastography
  - Liver biopsy

Younossi. Am J Gastroenterol. 2020;00:1.
## Commonly Used Noninvasive Tests

### Clinical or Laboratory Scores

- **Simple**
  - Fibrosis-4 (FIB-4)\(^{[1,2]}\)
  - NAFLD fibrosis score\(^{[1,2]}\)
  - AST/platelet ratio index\(^{[1]}\)

- **Proprietary**
  - Enhanced Liver Fibrosis Test\(^{[1]}\)
  - NIS4
  - ADAPT/Pro-C3\(^{[3]}\)
  - FibroSure\(^{[1]}\)
  - Hepascore

### Imaging

- Elastography
  - Transient elastography (eg, *FibroScan*)\(^{[1,2]}\)
  - 2D shear wave elastography\(^{[4]}\)
  - Magnetic resonance elastography\(^{[1]}\)
  - Corrected T1 (*Liver MultiScan*)\(^{[5,6]}\)
  - MRI-PDFF\(^{[7]}\)
  - FAST score\(^{[8]}\)

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Diagnosis of Fibrosis

- Diagnosis of Fibrosis is important as it is associated with long term outcomes
- US can identify fatty liver (steatosis), but cannot distinguish steatosis Vs NASH Vs Fibrosis (Early Cirrhosis)

- Simple tests (FIB-4, NFS, APRI)
  - Good NPV
  - Easily applicable
PRELHIN Study: Hepatic Fibrosis Associated With Long-term Outcomes in Patients With NAFLD

- Retrospective analysis in patients with NAFLD (N = 619); median follow-up: 12.6 yrs (range: 0.3-35.1)

Only fibrosis stage was associated with overall mortality, OLT, and liver-related events. Presence of NASH, NAS (or any of its components) had no independent prognostic effect.

Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4\(^1\)

Cutoff Scores for Measurement of Advanced Hepatic Fibrosis\(^2,3\)

<table>
<thead>
<tr>
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<th>FIB-4: ≤ 1.3</th>
<th>FIB-4: ≥ 2.67</th>
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<tbody>
<tr>
<td>NFS:</td>
<td>&lt; -1.455</td>
<td>&gt; 0.675</td>
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Absence of Advanced Fibrosis

Presence of Advanced Fibrosis

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Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4\(^1\)

Patients with advanced cirrhosis usually have a very low platelet count

FIB-4 Score < 1.3 NPV >95%
Rules out advanced fibrosis

FIB-4 Score >2.67 NPV 75%
Rules in advanced fibrosis

A low FIB-4 score indicates there is no advanced fibrosis and that liver biopsy is not needed
Vibration-Controlled Transient Elastography

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis)
  - The stiffer the liver, the faster the shear wave propagates
- Quick, bedside test (~ 5 mins)
- Limited by obesity, food intake, operator experience

Liver biopsy remains the gold standard for differentiating NAFL from NASH and staging liver fibrosis.

Proceed with liver biopsy if:

1. suspicion for NAFLD advanced fibrosis
2. concern for coexisting or competing etiology of chronic liver disease (B2).
LIVER BIOPSY

P: lipogranuloma
H: Mallory body
B: Balloon cell
Middle: PMNs
Bottom right: acidophil bodies
Liver Histology Grades

**Fibrosis Stage**

- **F0**: Normal
- **F1/2**: Perisinusoidal ± Portal
- **F3**: Bridging Fibrosis
- **F4**: Cirrhosis

**With VCTE:**

- Fibrosis unlikely with low value (< 6 kPa)
- Higher levels: Hepatitis, cholestasis, liver congestion, obesity, HCC
- Good correlation with portal pressure (20+ Kpa)
2D Shear Wave Elastography

- Ultrasound system, using real-time SWE map of liver elasticity to determine liver stiffness
  - 2D SWE color-coded map superimposed on B-mode image confirms readings are in liver, not in nearby vessels or kidneys
- May require radiologist/sonographer
- Liver elasticity measurements can be obtained in challenging cases of obesity

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<tr>
<td>2D-SWE stiffness &gt; 8.7 kPa</td>
<td>.973</td>
<td>.951</td>
<td>.98</td>
</tr>
</tbody>
</table>

Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD

<table>
<thead>
<tr>
<th>Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE stiffness &gt; 3.63 kPa</td>
<td>.86</td>
<td>.91</td>
<td>.924</td>
</tr>
</tbody>
</table>

## Diagnostic accuracy of non-invasive methods of fibrosis assessment

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Area under the Receiver Operating Curve (AUROC) for detection of moderate fibrosis</th>
<th>AUROC for detection of advanced Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD Fibrosis Score</td>
<td>0.82</td>
<td>0.86</td>
</tr>
<tr>
<td>FIB-4 Index</td>
<td>0.83</td>
<td>0.86</td>
</tr>
<tr>
<td>FibroScan</td>
<td>0.82</td>
<td>0.88</td>
</tr>
<tr>
<td>MR elastography</td>
<td>0.91</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Imajo et al. *Gastroenterology* 2016;150:626–637
Acute MI in the young; Lipid accumulation
LAL D

- Early identification
- Supportive care
  - Low fat diet
  - Statins
  - Evaluate for liver transplantation
- Enzyme replacement therapy with sebelipase alfa
Children and Adolescents

• Who should be screened for NAFLD and comorbidities?
  • Obesity or Type 2 DM
  • Adolescent females with polycystic ovary syndrome

• Diagnostic Approach
  • Screening using ALT
  • Next step: Imaging (US / MRI - PDFF)
  • Liver Biopsy in unclear cases and exclusion of other cause:
    • Wilson syndrome, mitochondrial disease, and medications.
Diagnosis of MAFLD
Risk factor + Diagnosis + CSPH + Complications

- Complications
  - Ascites
  - Variceal bleeding
  - Encephalopathy
  - HCC

N.B. HCC in NAFLD can occur in the absence of cirrhosis
• **VITAMIN E:**
  - NASH without T2DM or cirrhosis
  - Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis
  - S/Es: Hemorrhagic stroke, risk of prostate cancer?
  - No cardiac benefit
MEDICATIONS
NASH

• Pioglitazone 30-45 mg po/day
  • T2DM (FDA); NASH with and without T2DM
  • Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement?
  • Non liver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction, and stroke prevention
  • S/Es: weight gain, risk of heart failure exacerbation, bone loss in postmenopausal women
  • Has cardiac benefit
MEDICATIONS
NASH without cirrhosis

- Liraglutide 1.8 mg SC daily (T2DM) 0.6-3mg SC daily (obesity)
  - T2DM, Obesity (FDA); NASH without cirrhosis
  - Liver related: improves steatosis, no proven impact on fibrosis
  - Non liver related: improves insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease
  - S/Es: gastrointestinal, gallstones (related to weight loss), pancreatitis
  - Has cardiac benefit
MEDICATIONS
NASH without cirrhosis

• Semaglutide 0.4 mg SC daily, 0.25-2.4 mg SQ weekly
  • T2DM, Obesity (FDA); NASH without cirrhosis
  • Liver related: improves steatosis, NASH resolution, no proven impact on fibrosis (may slow)
  • Non liver related: improves insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease, stroke prevention
  • S/Es: gastrointestinal, gallstones (related to weight loss), pancreatitis
  • Has cardiac benefit
MEDICATIONS
T2DM or obesity with NAFLD

- **Tirzepatide**
  - T2DM (FDA)
  - Liver related: improves steatosis on imaging
  - Non liver related: improves insulin sensitivity, significant weight loss,
  - S/Es: gastrointestinal, gallstones (related to weight loss), pancreatitis
  - Unknown cardiac benefit
MEDICATIONS
T2DM or obesity with NAFLD

• **SGLT-2i**
  - T2DM (FDA)
  - Liver related: improves steatosis on imaging
  - Non liver related: improves insulin sensitivity, CV and renal outcomes; modest weight loss; benefit in heart failure
  - S/Es: genitourinary yeast infection, volume depletion, bone loss
  - Cardiac benefit
Diagnosis of MAFLD
Risk factor + Diagnosis + CSPH + Complications

- Complications
  - Ascites
  - Variceal bleeding
  - Encephalopathy
  - HCC

N.B. HCC in NAFLD can occur in the absence of cirrhosis
FRAX: FRACTURE RISK ASSESSMENT: BACK TO THE PATIENT
### FRAX: FRACTURE RISK ASSESSMENT

**Additional History:**
- Previous Fracture
- Parent Fracture Hip
- Current smoking
- Glucocorticoid
- Rheumatoid Arthritis
- Secondary osteoporosis

**Additional History:**
- Alcohol 3 or more units per day
- Femoral neck BMD

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**10 year risk:**
- Major osteoporotic 3.8%
- Hip fracture 1.6%

What is next?
If treatment is indicated, please click on the Treat item above to view guidance on related treatment options.
SUMMARY

- Identify high risk individuals for screening of MAFLD
- If patient has NAFLD/NASH, stratify based on the degree of Fibrosis
- Patients with Advanced Hepatic Fibrosis can quickly progress to Cirrhosis, HCC, Need of liver transplant, and poor Outcome
- FIB-4 marker considered as an initial NIT to assess for degree of fibrosis
- Aim for weight reduction
- New drugs in the horizon
THANK YOU

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