Improving Access to Quality Medical Care Webinar Series

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• Your phone &/or computer microphone has been muted
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“Non-Alcoholic Fatty Liver Disease (NAFLD)”

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Non-alcoholic fatty liver disease (NAFLD)

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Outline

• Definitions: NAFL vs NASH
• Prevalence and natural history
• Etiopathogenesis
• Association with systemic diseases
• Principles behind management and treatment guidelines
Definition

• NAFLD is characterized by excessive hepatic fat accumulation (>5%) associated with insulin resistance.

• Diagnosis requires exclusion of secondary causes and significant alcohol consumption (>21 drinks/week in men or >14 drinks/week in women OR >/=30g in men and >/=20g in women daily, about 10g alcohol/drink unit)
Table 2. The spectrum of NAFLD and concurrent diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subclassification</th>
<th>Most common concurrent diseases</th>
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<tbody>
<tr>
<td>NAFLD*</td>
<td>NAFL</td>
<td>° AFLD-Alcoholic fatty liver disease</td>
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<tr>
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<td>• Pure steatosis</td>
<td>° Drug-induced fatty liver disease</td>
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<td>• Steatosis and mild lobular inflammation</td>
<td>° Hepatitis C virus-associated fatty liver (genotype 3)</td>
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<tr>
<td>NASH</td>
<td>• Early NASH: no or mild (F0-F1) fibrosis</td>
<td>° Others</td>
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<td>• Fibrotic NASH: significant (≥F2) or advanced (≥F3,</td>
<td>• Haemochromatosis</td>
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<td>bridging) fibrosis</td>
<td>• Autoimmune hepatitis</td>
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<td></td>
<td>• NASH-Cirrhosis (F4)</td>
<td>• Coeliac disease</td>
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<td>• Wilson’s disease</td>
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<td>• A/hypo-beta-lipoproteinaemia lipoatrophy</td>
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<td>• Hypopituitarism, hypothyroidism</td>
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<td>• Starvation, parenteral nutrition</td>
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<td></td>
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<td>• Inborn errors of metabolism (Wolman disease [lysosomal acid lipase deficiency])</td>
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*EASL-EASD-EASO clinical practice guidelines for management of NAFLD. J Hepatol 2016;64:1388-1402
Spectrum of NAFLD

• NAFLD includes two pathologically distinct entities with different risk of progression and hepatocellular carcinoma (HCC)
  – Non-alcoholic fatty liver (NAFL)
  – Non-alcoholic steatohepatitis (NASH)
Pathologic definitions

- **NAFL**: Steatosis: Fat accumulation within the hepatocytes with or without lobular inflammation. >5% is abnormal

- **NASH**: Steatohepatitis: Evidence of hepatocellular injury in the form of ballooning degeneration in addition to steatosis and inflammation.
  - Ballooning is considered to be a result of oxidative stress, loss of intermediate filaments and fluid retention.

- Important to make the distinction as the prognosis is different
Macrovesicular Steatosis
Steatohepatitis
Fibrosis

Slowly progressive disease

– F1: Mild Perisinusoidal or periportal
– F2: Significant Both
– F3: Advanced Bridging
– F4: Cirrhosis Fibrosis with nodules
Cirrhosis
Natural history

• Risk of fibrosis progression is 1 stage in 14 years for NAFL and 7 years for NASH*

• Despite slow progression, once the disease progresses, complications and outcome are similar to other advanced liver diseases including complications due to cirrhosis and HCC.

*Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015; 13 (4) 643-54
Incidence and prevalence

- True incidence is not known
- Prevalence of NAFL
  - General population: 20-30% in Western and 5-18% in Asian population*.
  - In high risk population such as those undergoing bariatric surgery the prevalence is 73-91%*.
  - Prevalence is increasing.
- Prevalence of NASH
  - General population: 2-3%*
  - In high risk population such as those undergoing bariatric surgery the prevalence is 25-33%*

*Epidemiology and Natural History of NAFLD. Semin Liv Dis 2015;35:221-235
Pathogenesis: Unhealthy Lifestyle

• Unhealthy lifestyle plays a key role in development and progression of NAFLD
  – **Diet**: High calorie, excess saturated fats, refined carbohydrates, sugar-sweetened beverages, high fructose intake and Western diet

• Genetic modifiers have been identified:
  – PNPLA3
  – TM6SF2
Pathogenesis

OBESITY and INSULIN RESISTANCE

ADIPOSE TISSUE
- Lipolysis: Increased FFAs
- Release of proinflammatory cytokines and hormones

SKELETAL MUSCLE
- Hyperglycemia

LIVER
- Hyperglycemia
- Lipogenesis
- Increased FFA from adipose tissue
- Increased TG synthesis: Steatosis
- Pro-inflammation: Steatohepatitis

GUT MICROBIOME
- Endotoxemia
- Endogenous alcohol

Lifestyle Diet

GENETICS
- Lipotoxicity
- Pro-inflammation: Steatohepatitis
NAFLD is hepatic manifestation of systemic syndrome

NAFLD AND SYSTEMIC DISEASES
Systemic complications of NAFLD

- **Adipose Tissue IR** (VF, SCF)
  - Lipolysis
  - Inflammatory factors (TNFα, IL-1β, IL-6, MCP-1)
  - RBP-4
  - Leptin
  - Resistin
  - Adiponectin

- **Blood Vessels**
  - Atherosclerosis
    - LDLs
    - Ox-LDLs

- **Heart**
  - Early Cardiac Dysfunction

- **Pancreas**
  - Type 2 Diabetes

- **Kidney**
  - Chronic Kidney Disease

- **Gut**
  - Colorectal Cancer

- **Skeletal Muscle IR**
  - Hyperinsulinemia
  - Glucose disposal
  - Insulin levels

- **NAFLD**
  - FFA, glycerol
  - HGP, DNL, TG, VLDL, ROS
  - Hypercoagulation factors (PAI-1, F VII)
  - Inflammatory markers (CRP, MCP-1, TNF-α)
  - HDL-cholesterol

- **Dysbiosis Endotoxemia**
NAFLD and Type 2 Diabetes Mellitus

IR
T2DM
NAFLD
NAFLD and Type 2 Diabetes Mellitus

- NAFLD independently increases risk of T2DM.
- Regardless of other risk factors

- Steatosis $\rightarrow$ decreased insulin receptor substrate $\rightarrow$ decreased glycogen and increased glucose production $\rightarrow$ hyperglycemia
NAFLD and Type 2 Diabetes Mellitus

• Patients with NAFLD should be screened for T2DM and impaired glucose tolerance*
• Diabetics should be screened for presence of hepatic fat regardless of liver enzymes.*

• Once the patient diabetic:
  – May need higher doses of drugs to control glucose
  – Increased risk of microvascular complications
  – Increased risk of liver-related complications such as cirrhosis and HCC

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NAFLD and cardiovascular diseases

• Increased risk of cardiovascular diseases (2/2 atherosclerosis) and cardiac dysfunction (2/2 fat deposition around heart): No.1 cause of mortality in NAFLD patients

• Rate of fibrosis progression is doubled by arterial hypertension

• Recommendation: Screening of cardiovascular disease risk factors in all patients*

*EASL-EASD-EASO clinical practice guidelines for management of NAFLD. J Hepatol 2016;64:1388-1402
NAFLD and other diseases

• Chronic kidney disease
• Systemic cancers:
  – GI (liver, colon, esophagus, stomach and pancreas)
  – Extraintestinal (kidney in men and breast in women)
Causes of mortality

• The top 3 causes of mortality in NAFLD patients are:
  1. Cardiovascular diseases
  2. Non-liver cancers
  3. Liver-related complications
Disclaimer: I am not a hepatologist!

MANAGEMENT
EASL recommendation

• Patients with metabolic risk factors should undergo diagnostic procedures for diagnosis of NAFLD (relies on demonstration of excessive liver fat) and vice-versa

• Exclude secondary causes of steatosis

• Exclude concurrent other liver diseases
Metabolic risk factors

- Obesity
- Metabolic syndrome (MetS): Presence of any 3 of the following 5 (associated with IR):
  1. Impaired fasting glucose or T2DM
  2. Hypertriglyceridemia
  3. Low HDL-cholesterol
  4. Increased waist circumference
  5. Hypertension
• Assessment of dietary and physical activity habits is a key component of NAFLD screening and management.
Non-invasive Detection of Steatosis

• Imaging: Ultrasound is widely available and affordable option. However, conventional imaging has low sensitivity for <30% fat detection

• Serum biomarkers: Available but not very popular. Low sensitivity for lower fat content.
Detection of steatohepatitis

- Liver biopsy is the only modality that can reliably identify steatohepatitis.

- Clinical, biochemical and imaging parameters do not identify NASH. Non-invasive tests including CK18 have not been validated for use in clinical practice.

- Important to recognize as it predisposes to fibrosis
Detection of fibrosis

• Most important prognostic factor
• Correlates with liver-related outcome and mortality
• Presence of advanced fibrosis warrants specialized hepatological investigation and management
Non-invasive tests to detect fibrosis

• Many serum biomarkers and imaging techniques are available. All perform better to identify advanced fibrosis. Hence, these tests can be reliably used to exclude advanced fibrosis.
Table 3. Protocol for a comprehensive evaluation of suspected NAFLD patients.

<table>
<thead>
<tr>
<th>Level</th>
<th>Variable</th>
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<tbody>
<tr>
<td>Initial</td>
<td>1. Alcohol intake: &lt;20 g/day (women), &lt;30 g/day (men)</td>
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<td>2. Personal and family history of diabetes, hypertension and CVD</td>
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<td>3. BMI, waist circumference, change in body weight</td>
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<td>4. Hepatitis B/Hepatitis C virus infection</td>
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<td>5. History of steatosis-associated drugs</td>
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<td>6. Liver enzymes (aspartate and alanine transaminases</td>
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<td>( \gamma )-glutamyl-trans-peptidase)</td>
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<td></td>
<td>7. Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR])</td>
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<td>8. Complete blood count</td>
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<td>9. Serum total and HDL-cholesterol, triacylglycerol, uric acid</td>
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<td></td>
<td>10. Ultrasonography (if suspected for raised liver enzymes)</td>
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<td>Extended *</td>
<td>1. Ferritin and transferrin saturation</td>
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<td></td>
<td>2. Tests for coeliac and thyroid diseases, polycystic ovary syndrome</td>
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<tr>
<td></td>
<td>3. Tests for rare liver diseases (Wilson, autoimmune disease, ( \alpha_1 )-antitrypsin deficiency)</td>
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</tbody>
</table>

*According to a priori probability or clinical evaluation.

*EASL-EASD-EASO clinical practice guidelines for management of NAFLD. J Hepatol 2016;64:1388-1402
Metabolic risk factors present

Ultrasound (steatosis biomarkers¹)/Liver enzymes²

Steatosis present
Normal liver enzymes
Serum fibrosis markers⁴
Low risk⁵ Follow-up/2 years
Liver enzymes, fibrosis biomarkers

Abnormal³ liver enzymes
Identify other chronic liver diseases
In-depth assessment of disease severity
Decision to perform liver biopsy
Initiate monitoring/therapy

Steatosis absent
Normal liver enzymes
Follow-up/3-5 years

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NAFLD and HCC

- Increased risk of HCC
- Lower prevalence of cirrhosis than non-NAFLD related HCC
- HCC screening is difficult due to large number of cases
- Screening in NAFLD-cirrhosis. No recommendations for non-cirrhotic
TREATMENT
Diet and lifestyle changes

• Cornerstone of Rx: Multiple studies have shown benefit.

• **Diet**: Calorie restriction and exclusion of foods such as processed food, high in fructose. Mediterranean diet has been shown to be beneficial

• **Exercise**: Aerobic and resistance training have been found to be equally effective.

• **Behavioral restructuring** such as cognitive therapy for long term, sustained benefit.
Pharmacotherapy

• Vitamin E and Pioglitazone:
  – Approved for select group of patients (non-diabetic, no cirrhosis).
  – Long term safety concerns

• Multiple on-going clinical trials
Take home points

• NAFLD is a slowly progressive disease
• Closely associated with metabolic risk factors
• Important to identify and treat other systemic diseases that are often co-existent
• Diet and unhealthy lifestyle are key etiologic factors. Modification of dietary practices and lifestyle changes are cornerstone of management
Thank you!

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