Improving Access to Quality Medical Care Webinar Series

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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.

Disease	Subclassification	Most common concurrent diseases
NAFLD*	NAFL • Pure steatosis • Steatosis and mild lobular inflammation	° AFLD-Alcoholic fatty liver disease ° Drug-induced fatty liver disease ° Hepatitis C virus-associated fatty liver (genotype 3) ° Others • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson's disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism (Wolman disease [lysosomal acid lipase deficiency])
	NASH • Early NASH: no or mild (F0-F1) fibrosis • Fibrotic NASH: significant (≥F2) or advanced (≥F3, bridging) fibrosis • NASH-Cirrhosis (F4)	
	Hepatocellular carcinoma^	

*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)

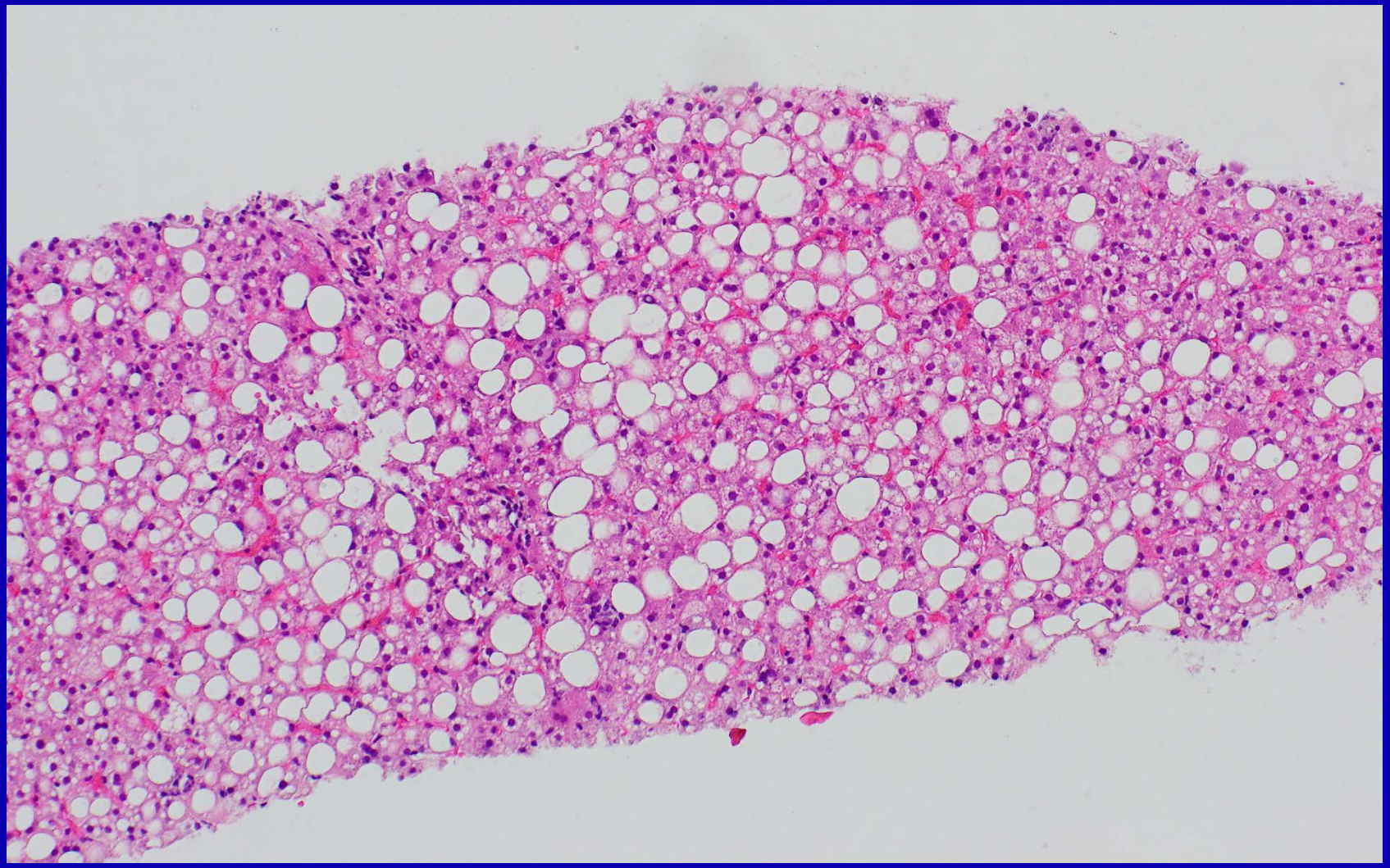
Pathologic definitions

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

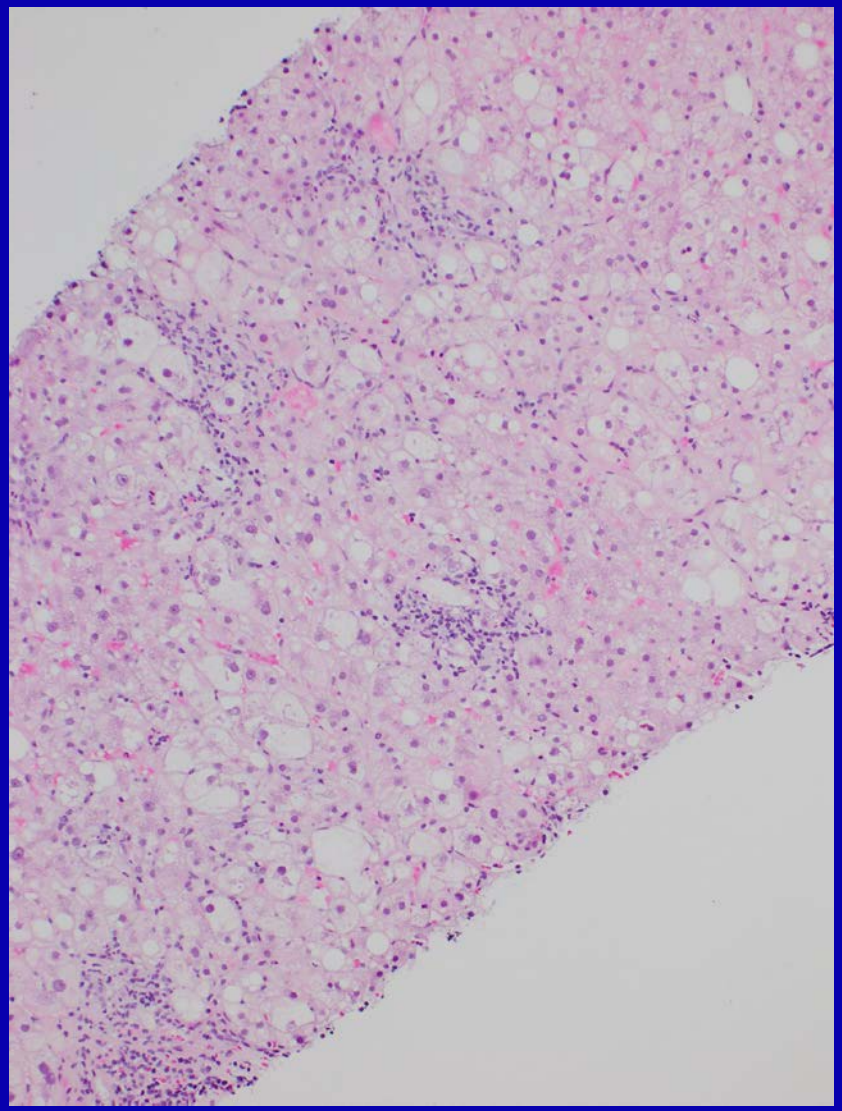
- **NASH**: Steatohepatitis: Evidence of hepatocellular injury in the form of ballooning degeneration in addition to steatosis and inflammation.
  - Ballooning is considered to be a result of oxidative stress, loss of intermediate filaments and fluid retention.

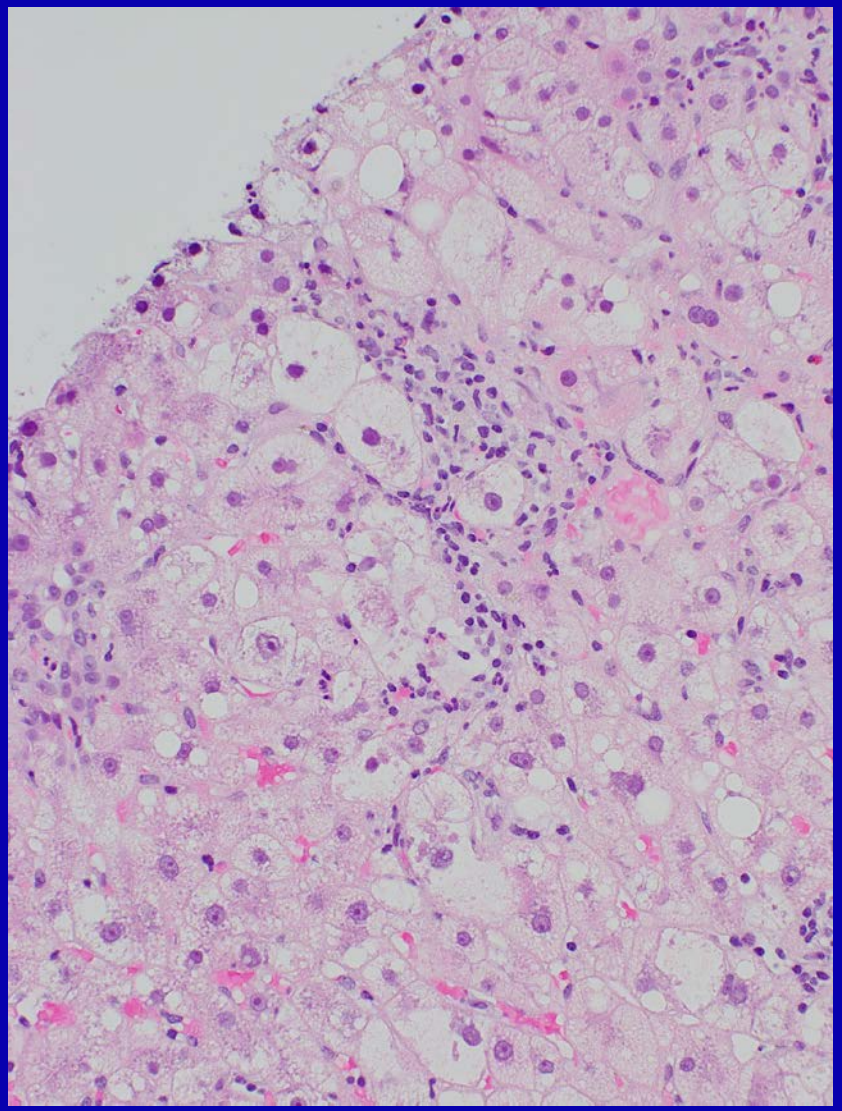
- Important to make the distinction as the prognosis is different

Macrovesicular Steatosis



Steatohepatitis



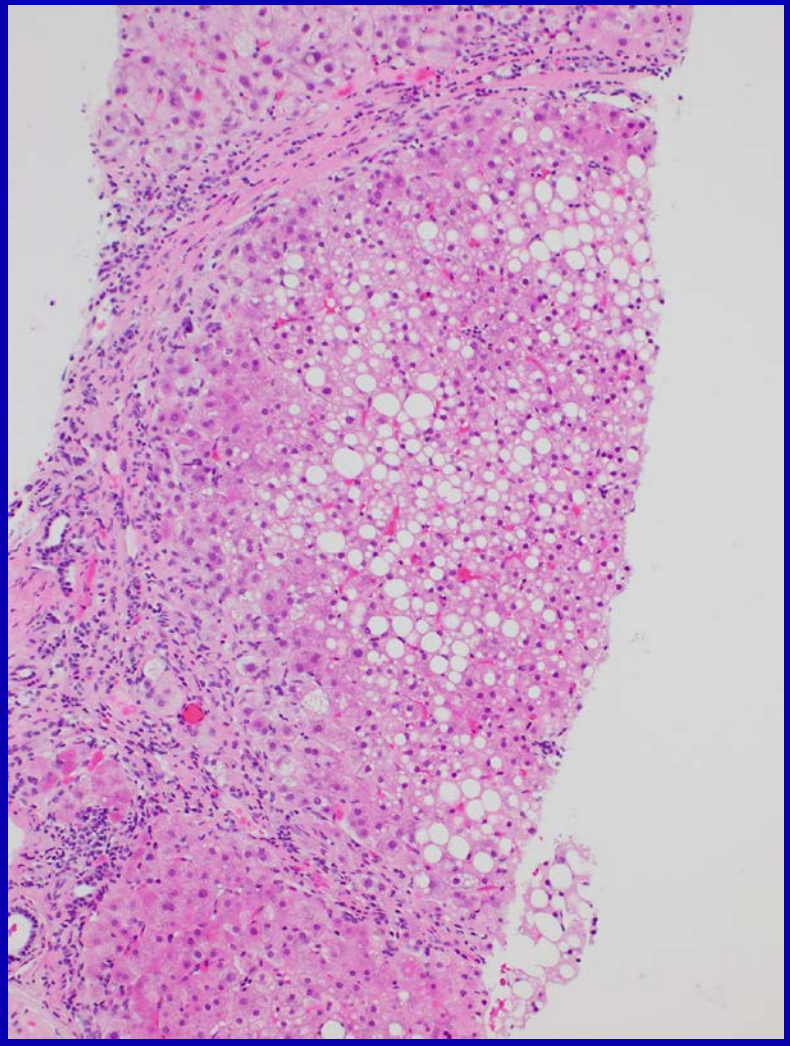


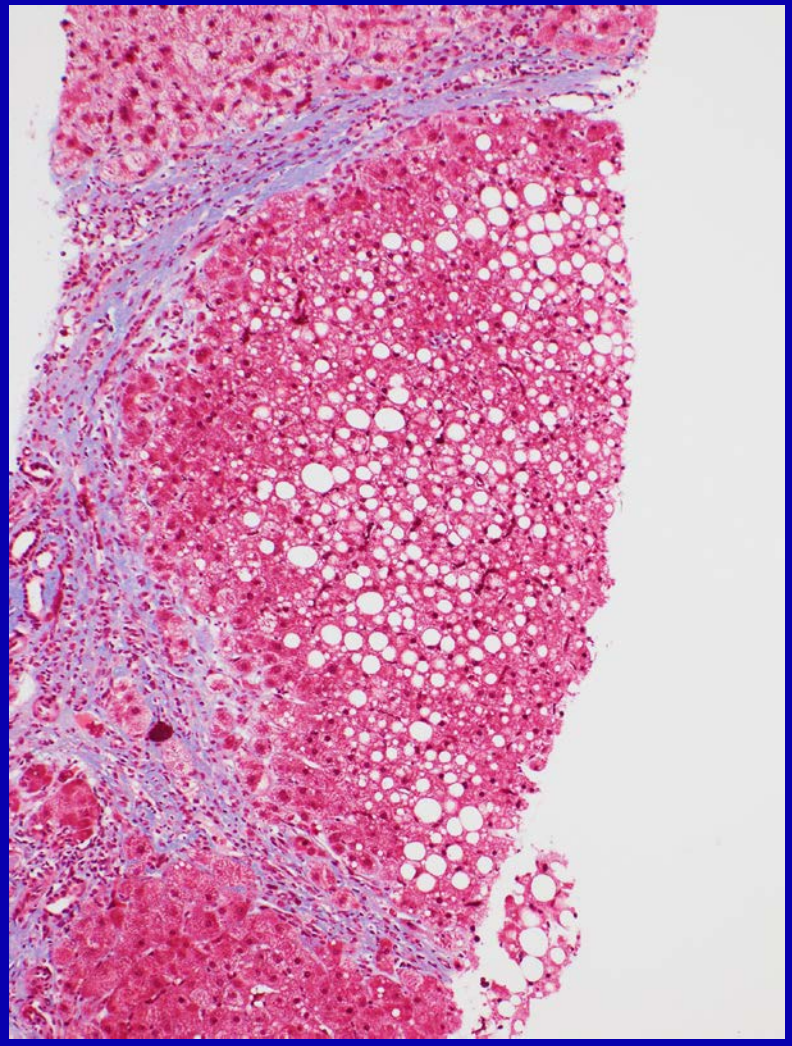
Fibrosis

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%*

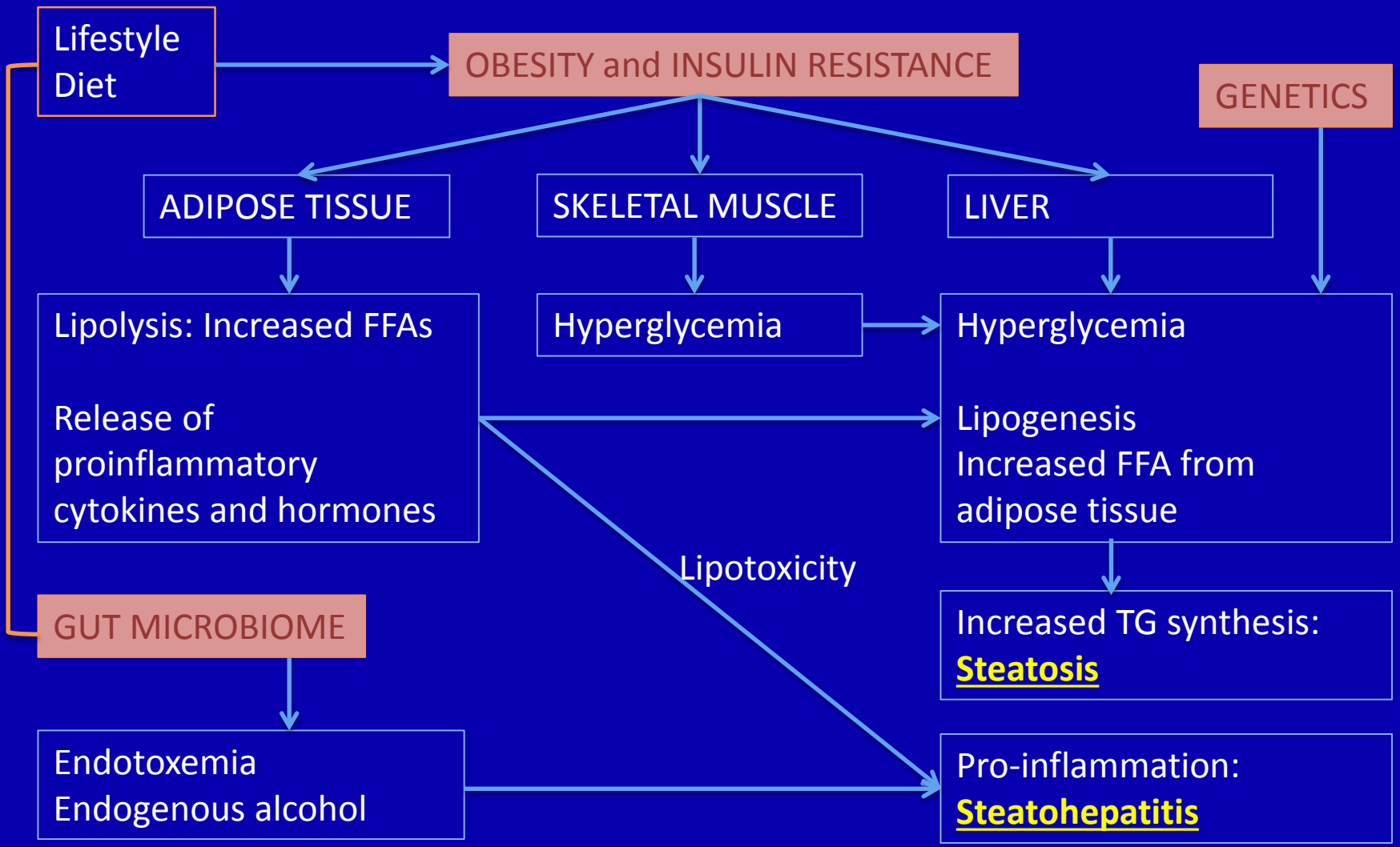
*Epidemiology and Natural History of NAFLD. Semin Liv Dis 2015;35:221-235

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

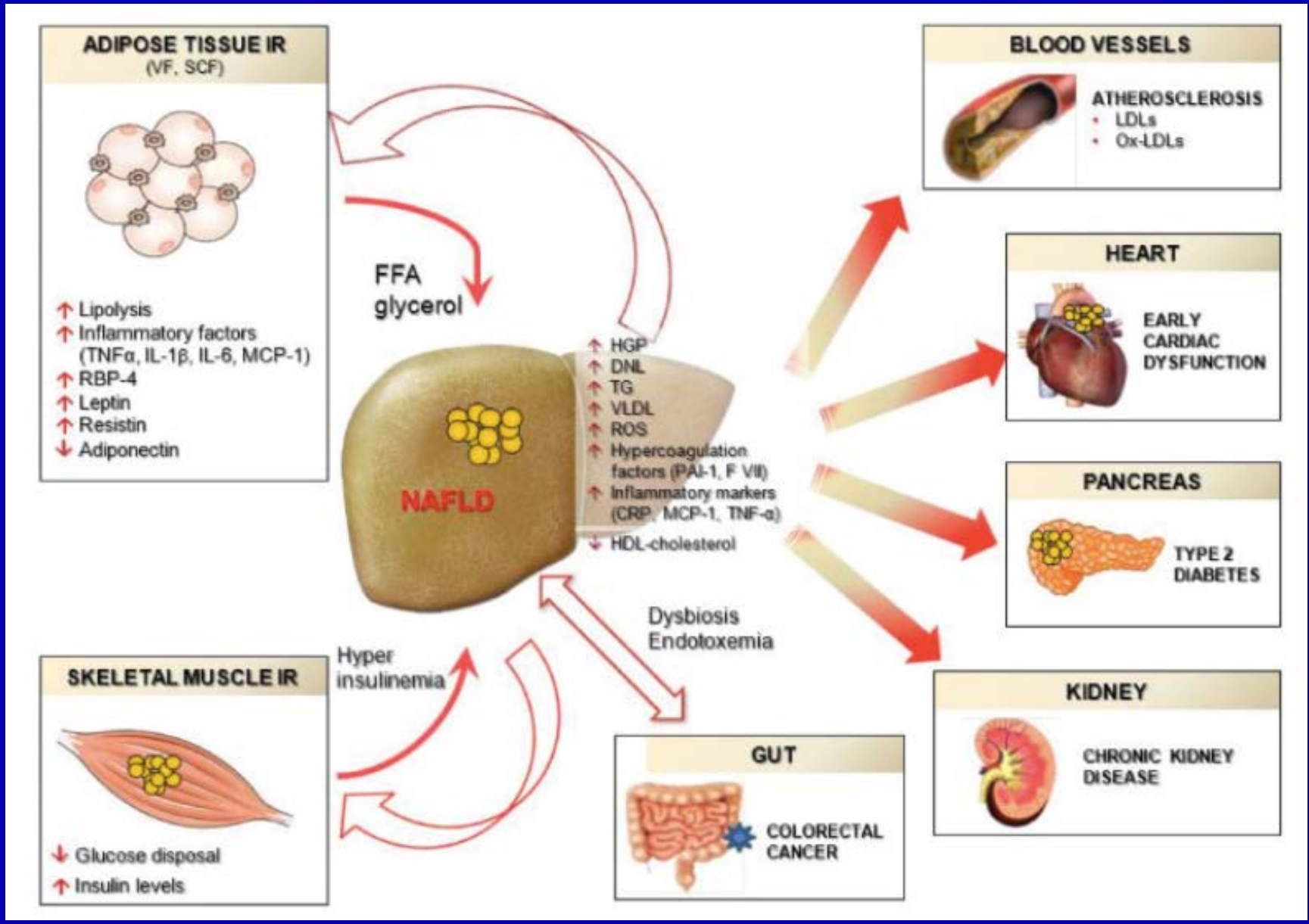
Pathogenesis



NAFLD is hepatic manifestation of systemic syndrome

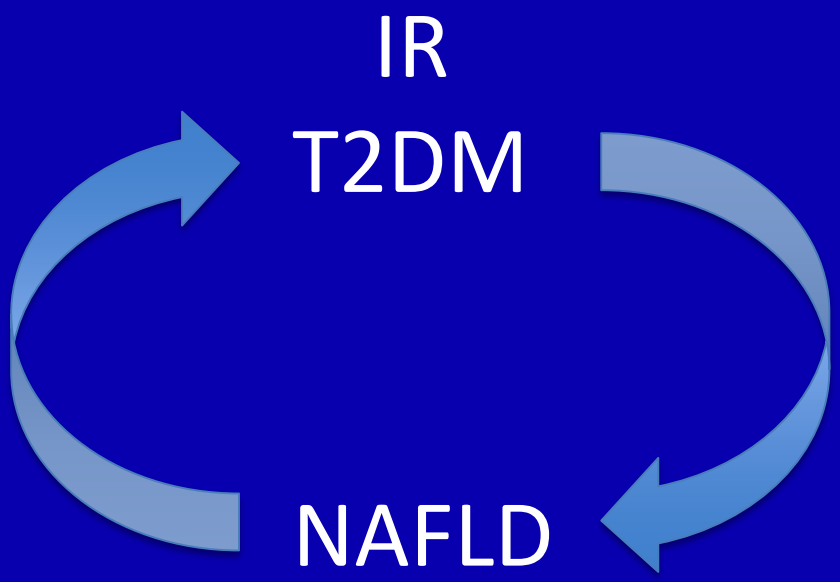
NAFLD AND SYSTEMIC DISEASES

Systemic complications of NAFLD



Vanni et al. Semin Liv Dis 2015;35:236-249

NAFLD and Type 2 Diabetes Mellitus



NAFLD and Type 2 Diabetes Mellitus

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

- Steatosis → decreased insulin receptor substrate → decreased glycogen and increased glucose production→ 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

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

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

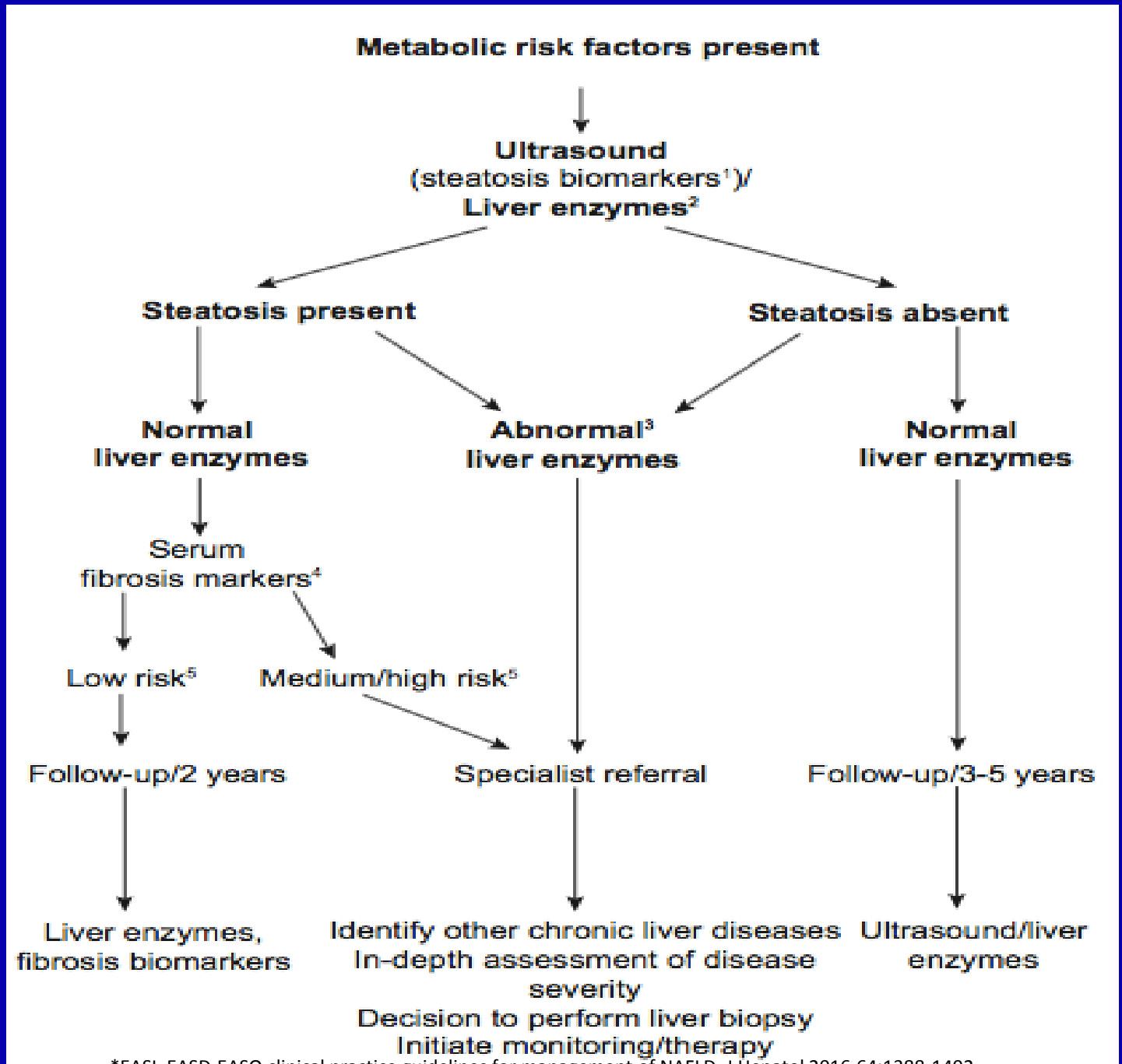
- Many serum biomarkers and imaging techniques are available. All perform better to identify advanced fibrosis. Hence, these tests can be reliably used to exclude advanced fibrosis.

Table 3. Protocol for a comprehensive evaluation of suspected NAFLD patients.

Level	Variable	
Initial	1.	Alcohol intake: <20 g/day (women), <30 g/day (men)
	2.	Personal and family history of diabetes, hypertension and CVD
	3.	BMI, waist circumference, change in body weight
	4.	Hepatitis B/Hepatitis C virus infection
	5.	History of steatosis-associated drugs
	6.	Liver enzymes (aspartate and alanine transaminases (γ-glutamyl-trans-peptidase))
	7.	Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR])
	8.	Complete blood count
	9.	Serum total and HDL-cholesterol, triacylglycerol, uric acid
	10.	Ultrasonography (if suspected for raised liver enzymes)
Extended *	1.	Ferritin and transferrin saturation
	2.	Tests for coeliac and thyroid diseases, polycystic ovary syndrome
	3.	Tests for rare liver diseases (Wilson, autoimmune disease, α1-antitrypsin deficiency)

*According to a priori probability or clinical evaluation.

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



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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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