# NON-ALCOHOLIC FATTY LIVER DISEASE

# (NAFLD)

**By Dr. M. Ghezlou**

**(Gastroentrologist and Hepatologist)**

# DEFINITION

***Nonalcoholic fatty liver disease(NAFLD) :***

- ✓ ***Fat accumulation*** **in the liver exceeding** ***5%*** **of its weight.**
- ✓ **Evidence of** ***hepatic steatosis*****, either by** ***imaging*** **or by** ***histology***
- ✓ ***No*** **causes for** ***secondary*** **hepatic fat accumulation**

# CAUSES OF SECONDARY H.STEATOSIS

**Macrovesicular steatosis**

- alcohol consumption
- Hepatitis C
- Wilson Disease
- Lipodystrophy
- Starvation
- Parenteral nutrition

Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

***Microvascular steatosis***

- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism

# PATHOGENESIS

***Insulin resistance*** **is related to** ***obesity*** **and is** ***central*** **to the pathogenesis of NAFLD.**

**In addition,** ***oxidative stress*** **and** ***cytokines*** **are important contributing factors,**

***Together resulting in :***
***steatosis*** **and** ***progressive liver damage*** **in genetically susceptible individuals.**

# NAFLD AND RELATED *DEFINITIONS*

- **Nonalcoholic Fatty Liver Disease ( NAFLD ):**

- includes the ***entire spectrum of fatty liver disease*** in individuals ***without*** significant ***alcohol consumption***, ranging from fatty liver to steatohepatitis and cirrhosis.

Normal liver ⟷ Steatosis ⟷ NASH ⟶ Fibrosis

# NAFLD AND RELATED *DEFINITIONS*

## ❑ Nonalcoholic Fatty Liver ( NAFL ):

- ***hepatic steatosis*** *without evidence of* ***hepatocellular injury*** in the form of ***ballooning*** of the hepatocytes or no evidence of ***fibrosis.*** The risk of progression to cirrhosis and liver failure is minimal.

# NAFLD AND RELATED *DEFINITIONS*

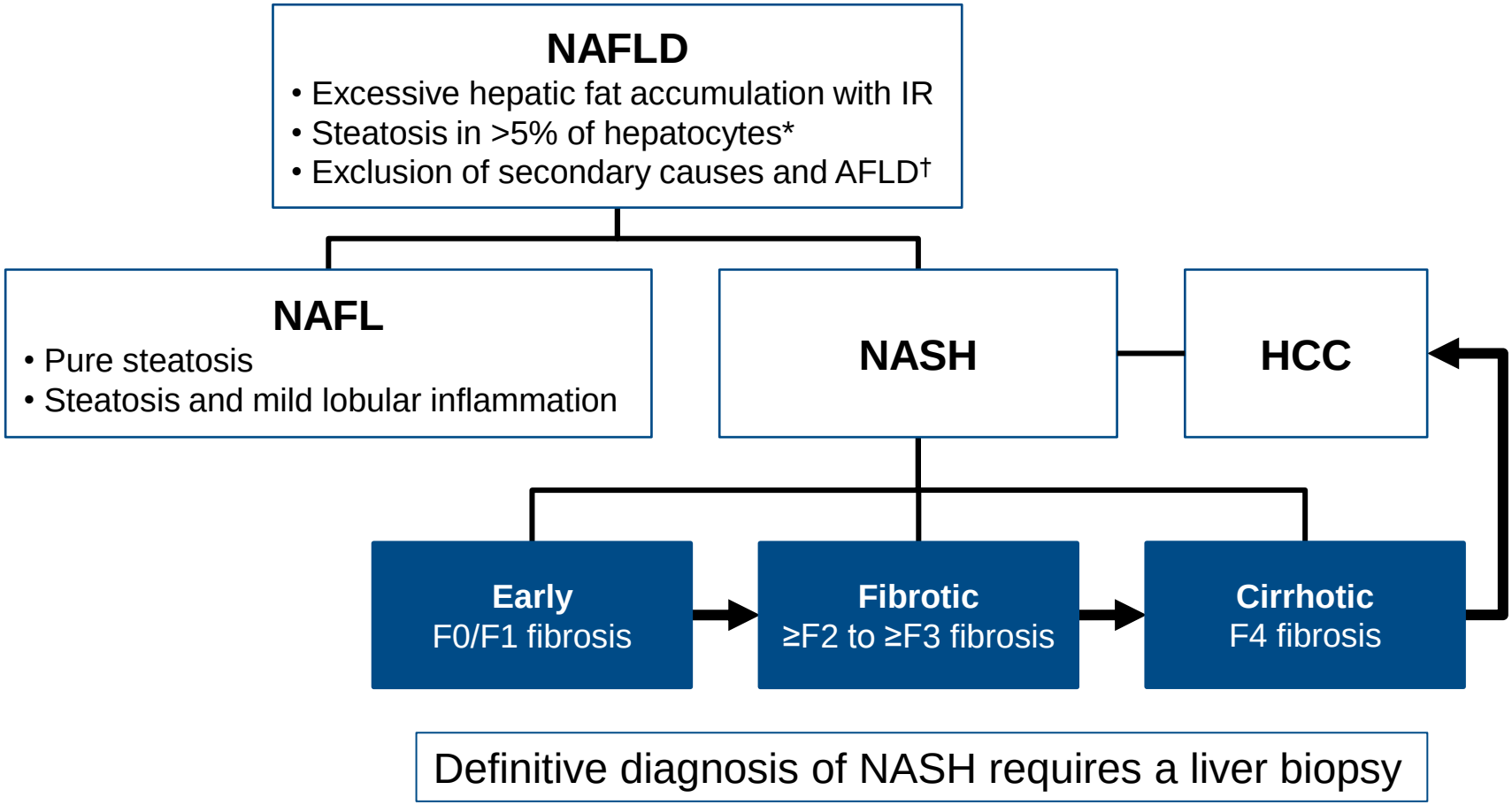
## ❑Nonalcoholic steatohepatitis (NASH):

- ***hepatic steatosis*** *and* ***inflammation*** *with hepatocyte injury*
- *(ballooning) with or without fibrosis .*
- *This can progress to* ***cirrhosis***, ***liver failure*** *and rarely* ***liver cancer***.

## ❑ NASH Cirrhosis :

- *Presence of* ***cirrhosis*** *with current or previous histological evidence of steatosis or steatohepatitis.*

# Definitions of NAFLD, NAFL and NASH




*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

EASL™
The Home of Hepatology

# PATIENT SYMPTOMS

**In most cases, NASH does *not cause any specific symptoms.***

**There are sometimes vague symptoms of**

**fatigue, malaise, and abdominal discomfort.**

# *PREVALENCE*

- The meta-analysis estimated that the ***overall global prevalence*** of NAFLD diagnosed by imaging is around **25%**

- The ***highest prevalence*** of NAFLD is reported from the Middle East 32% and ***South America*** 30%

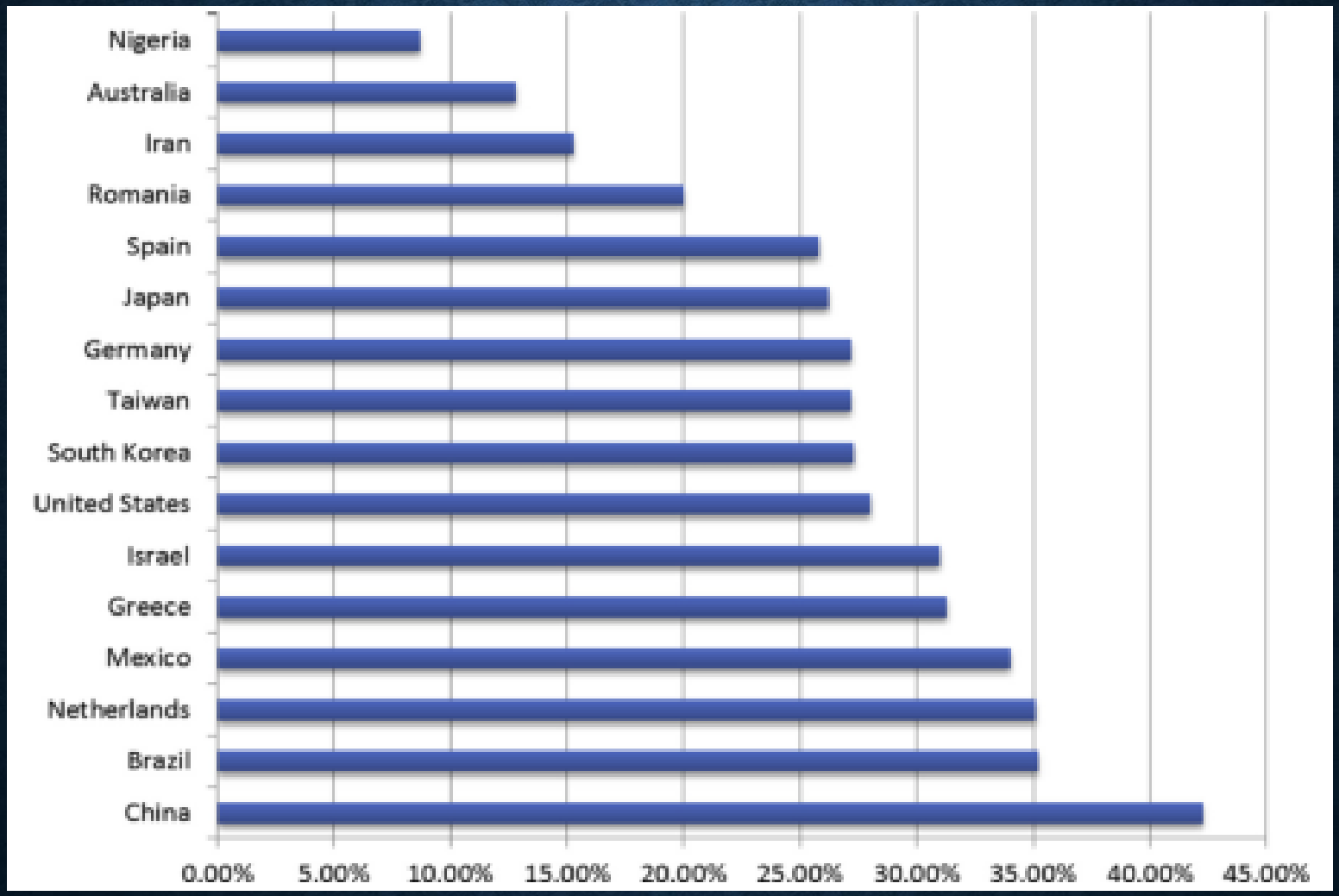
- the ***lowest prevalence*** rate is reported from **Africa 13%**

# EPIDEMIOLOGY

- NAFLD is the ***most common chronic liver disease*** in Western countries .

- **20% to 30%** of ***adults***.
- **10-15%** of NAFL develop ***NASH***
- **Up to 20%** of NASH will progress to ***cirrhosis***

- ***75% of obese*** have ***NAFLD***
- ***20%*** may have ***NASH***




**Global prevalence of NAFLD**

# ***EPIDEMIOLOGY***

- both the prevalence of NAFLD and stage of liver disease appear to increase with ***age***.

- ***male sex*** has been considered a risk factor for NAFLD.

- the prevalence of NAFLD ***in men is 2 times*** higher than in women.

# RISK FACTORS ASSOCIATED WITH NAFLD

Common Conditions With Established Association

- ***Obesity***
- ***T2DM***
- ***Dyslipidemia***
- ***Metabolic syndrome***
- ***Polycystic ovary syndrome***

***Other Conditions Associated With NAFLD***

- ***Hypothyroidism***
- ***Obstructive sleep apnea***
- ***Hypopituitarism***
- ***Hypogonadism***
- ***Pancreatoduodenal resection***
- ***Psoriasis***

Table 6 Risk factors and associated conditions

| Risk factors | Disease progression | Associated conditions |
|---|---|---|
| • Insulin resistance/metabolic syndrome<br>• Jejunoileal bypass surgery<br>• Age—highest risk in 40–65-year-olds, but it does occur in children < 10 y old<br>• Ethnicity—higher risk in Hispanics and Asians, lower risk in African-Americans<br>• Positive family history—genetic predisposition<br>• Drugs and toxins—e.g., amiodarone, coralgil, tamoxifen, perhexiline maleate, corticosteroids, synthetic estrogens, methotrexate, IV tetracycline, highly active antiretroviral drugs (HAART) | • Obesity, Increased BMI and waist circumference<br>• Uncontrolled diabetes, hyperglycemia, hypertriglyceridemia<br>• Sedentary lifestyle, lack of exercise<br>• Insulin resistance<br>• Metabolic syndrome<br>• Age<br>• Genetic factors | • Hyperlipidemia<br>• Insulin resistance/metabolic syndrome<br>• Type 2 diabetes<br>• Hepatitis C<br>• Rapid weight loss<br>• Total parenteral nutrition<br>• Wilson's disease, Weber–Christian disease, a beta lipoproteinemia, diverticulosis, polycystic ovary syndrome, obstructive sleep apnea |

# METABOLIC SYNDROME

The presence of ***three or more*** of the following features:

***I.*** ***Wist circumference*** greater than 102 cm in men or greater than 88 cm in women; (EASL:94-80cm)

II. ***TG*** level 150 mg/dL or greater;

***III.*** ***HDL cholesterol*** level less than 40 mg/dL in men and less than ***50 mg/dL*** in women;

IV. **Systolic *Blood pressure:*** 130 mm Hg or greater or ***Diastolic Blood pressure:*** 85 mm Hg or greater;

I. ***FBS level*** 110 mg/dL or greater (EASL:100mg/dL)

# NATURAL HISTORY OF NAFLD

**Patients with NAFLD have *increased overall mortality* compared to matched control populations without NAFLD.**

**The most common cause of death in patients with NAFLD is *cardiovascular disease (CVD),* independent of other metabolic comorbidities.**

# NATURAL HISTORY OF NAFLD

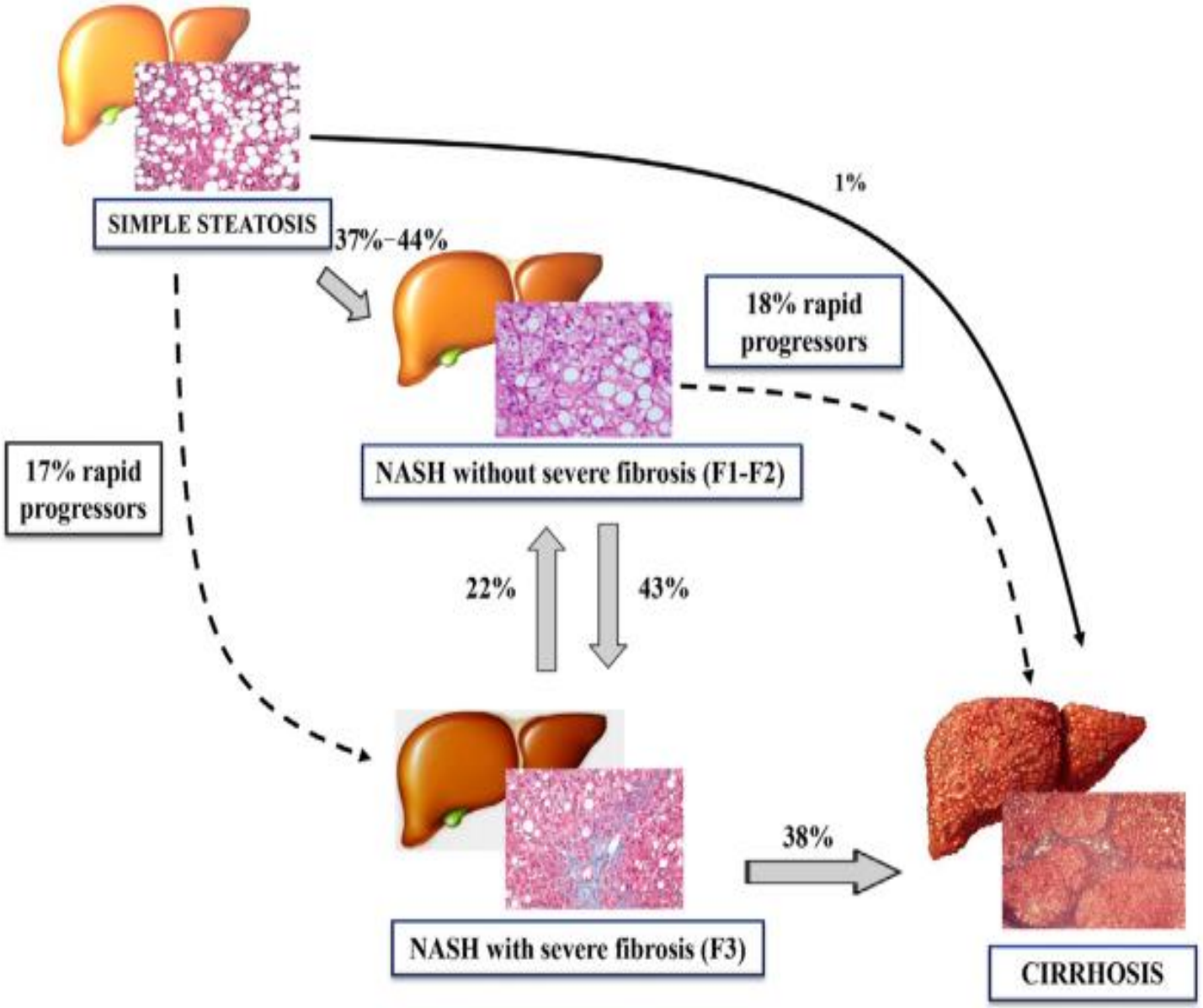
***liver-related mortality :***

**is the 12th leading cause of death in the general population,**

**it is the *second or third* cause of death among patients with *NAFLD.***

**NAFLD is now considered the third-most common cause of hepatocellular carcinoma (HCC) in the United States.**

# Progression and Natural History



- Causes of mortality in cirrhotic NASH patients:
  - — Liver failure
  - — Sepsis
  - — Variceal hemorrhage
  - — HCC
  - — Cardiovascular disease
- Independent predictors for progression of fibrosis:
  - — Age > 45–50
  - — BMI > 28–30 kg/m2
  - — Degree of insulin resistance
  - — Diabetes
  - — Hypertension
- Negative impact on NASH survival:
  - — Diabetes and elevated ALT and AST
  - — Older age and presence of necrotic inflammation on initial liver biopsy

# EVALUATION OF INCIDENTALLY DISCOVERED

# HEPATIC STEATOSIS(HS)

**Patients with *incidental HS* detected on imaging who lack any liver-related symptoms or signs and have *normal liver biochemistries* should be assessed for:**

***metabolic risk factors*** **and**
***alternate causes for HS*** **such as significant alcohol consumption or *medications.***

# SCREENING FOR NAFLD IN PRIMARY CARE, DIABETES, AND OBESITY CLINICS

**There should be a *high index of suspicion* for NAFLD and NASH in patients with *type 2 diabetes.***

# SCREENING OF FAMILY MEMBERS

**Systematic screening of family members for NAFLD is *not recommended* currently**

# DIAGNOSIS

The presence of ***any of the following***, especially ***with a history of abnormal AST/ALT,*** should lead to a work-up for NAFLD/NASH:

Chronic elevation of AST/ALT PLUS

— Presence of obesity, especially morbid obesity (BMI > 35)
— Diagnosis of type 2 diabetes mellitus
— Diagnosis of metabolic syndrome
— History of obstructive sleep apnea
— Presence of insulin resistance

# MUST BE EXCLUDED

**Viral hepatitis:**

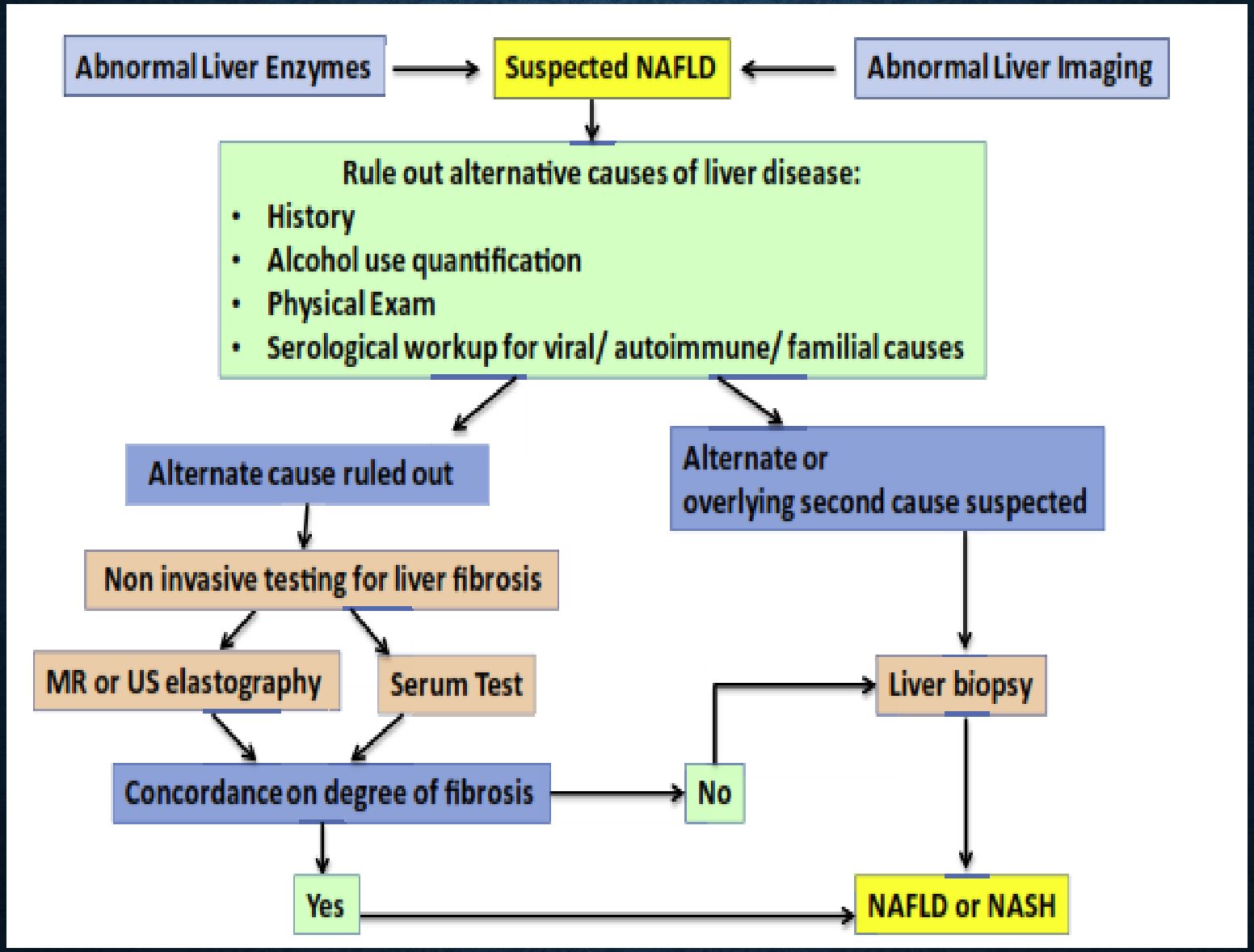
hepatitis B surface antigen, hepatitis C virus antibody or HCVRNA, hepatitis A antibody IgM, hepatitis E antibody; it should be noted that the patient may have coexisting viral hepatitis as well as NAFLD/NASH.

Alcohol-related liver disease including alcoholic steatohepatitis.

Autoimmune liver disease.

Congenital causes of chronic liver disease:
hereditary hemochromatosis Wilson's disease,
alpha-1-antitrypsin deficiency PCOD

Drug-induced liver disease.




**Investigating a patient with NAFLD.**

# LIVER BIOPSY

***Although it is invasive and has a potential for sampling errors and inconsistent interpretation of the histopathology***

***liver biopsy is required in order to establish the diagnosis and to stage NASH.***

***There is no reliable way of distinguishing between NAFLD/ALD and NASH/ASH without a liver biopsy.***

# WHEN TO OBTAIN A LIVER BIOPSY IN PATIENTS WITH NAFL

***Liver biopsy should be considered*** **in patients with NAFLD who are at increased risk of having SH and/or advanced fibrosis.**

***The presence of :*** **MetS, NFS or FIB-4, or liver stiffness measured by VCTE or MRE may be used for identifying patients who are *at risk for SH and/or advanced fibrosis.***

***Liver biopsy should be considered*** **in patients with suspected NAFLD in whom *competing etiologies* for HS and the presence and/or severity of *coexisting CLDs* cannot be excluded without a liver biopsy.**

# LIMITATIONS OF LIVER BIOPSY

- Poor patient ***compliance***
- Limited usefulness for ***dynamic follow-up***
- Risk of ***complications*** typical of invasive procedures (Pain, bleeding, mortality)
- ***Sampling errors***

# NON INVASIVE ASSESSMENT

## OF STEATOHEPATITIS AND ADVANCED FIBROSIS

In patients with NAFLD, **MetS** predicts the presence of **SH,** and its presence can be used to target patients for a liver biopsy.

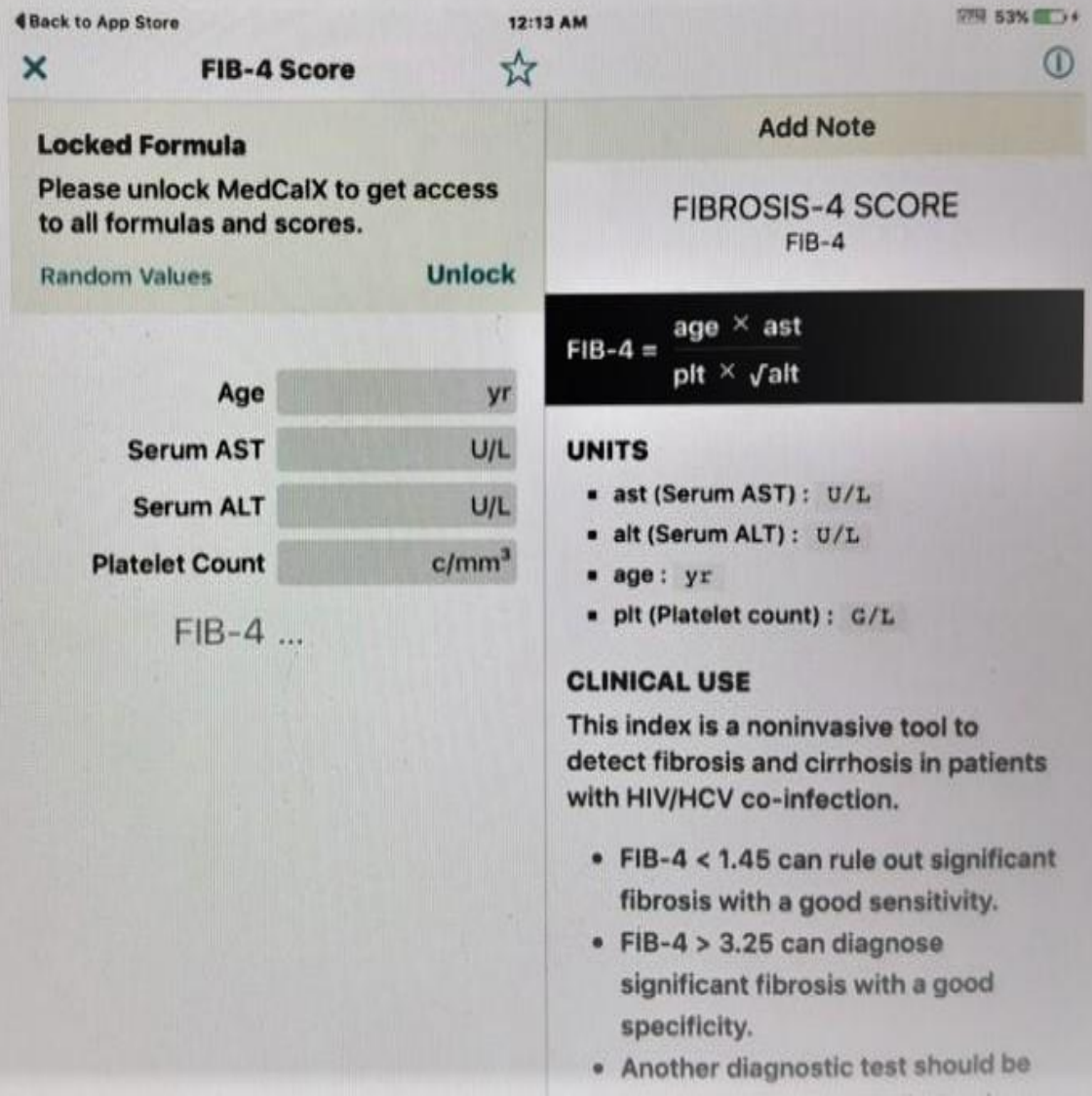
***NFS*** or ***FIB-4*** index are clinically useful tools for identifying NAFLD patients with higher likelihood of having ***bridging fibrosis*** or ***cirrhosis***

***Transient Elastography*** or ***MRE*** are clinically useful tools for identifying advanced fibrosis in patients with NAFLD.

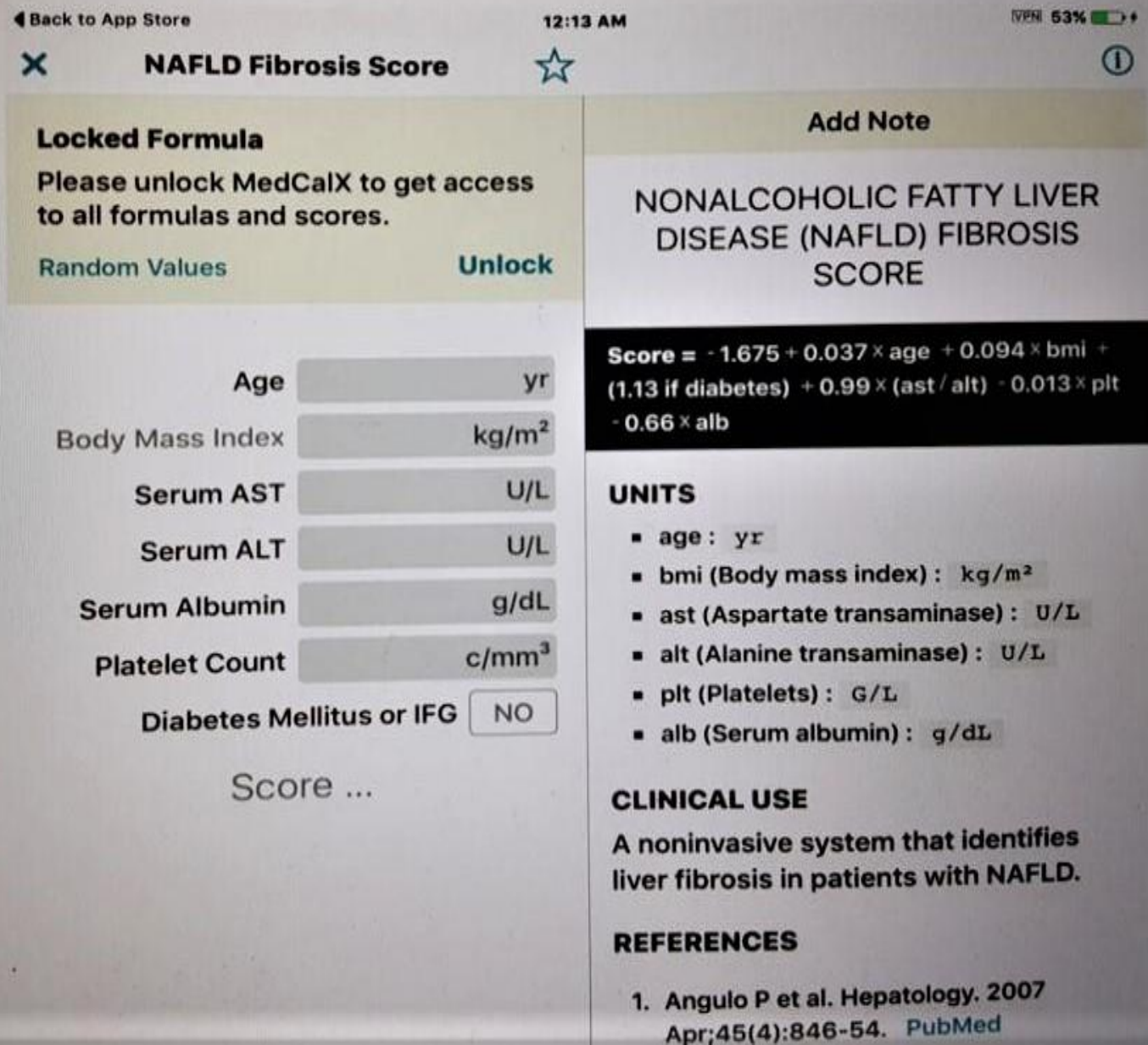
# *DISEASE STAGE CAN BE ASSESSED USING:*

- Vibration-Controlled Transient Elastography ***(VCTE)***
- Fibrosis-4 index ***(FIB4)***
- NAFLD Fibrosis Score ***(NFS)***
- Aspartate aminotransferase (AST) to platelet ratio index ***(APRI)***

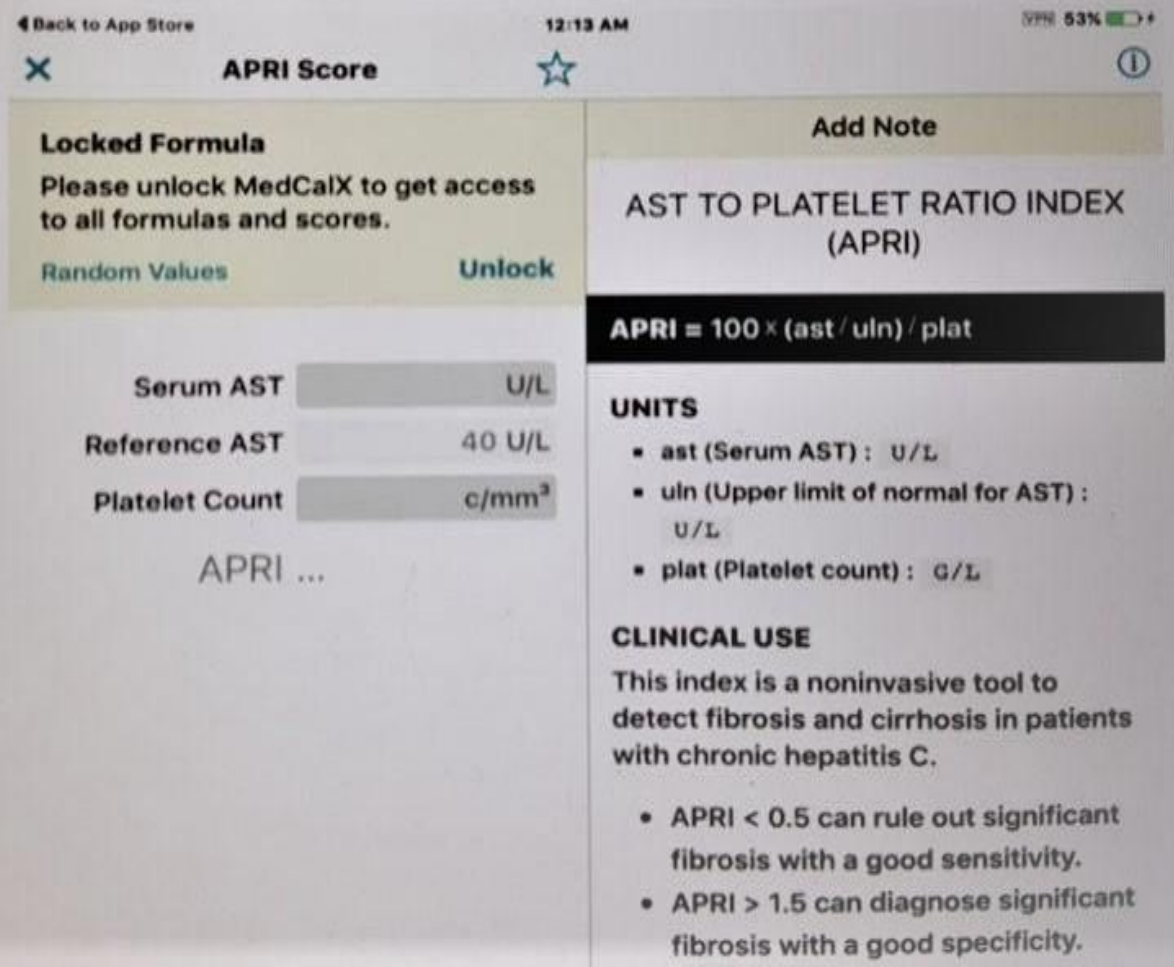
# Fibrosis-4 (FIB4) index



# NAFLD Fibrosis Score (NFS)



# Aspartate aminotransferase (AST) to platelet ratio index (APRI)



# *VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY*

# *(VCTE)*

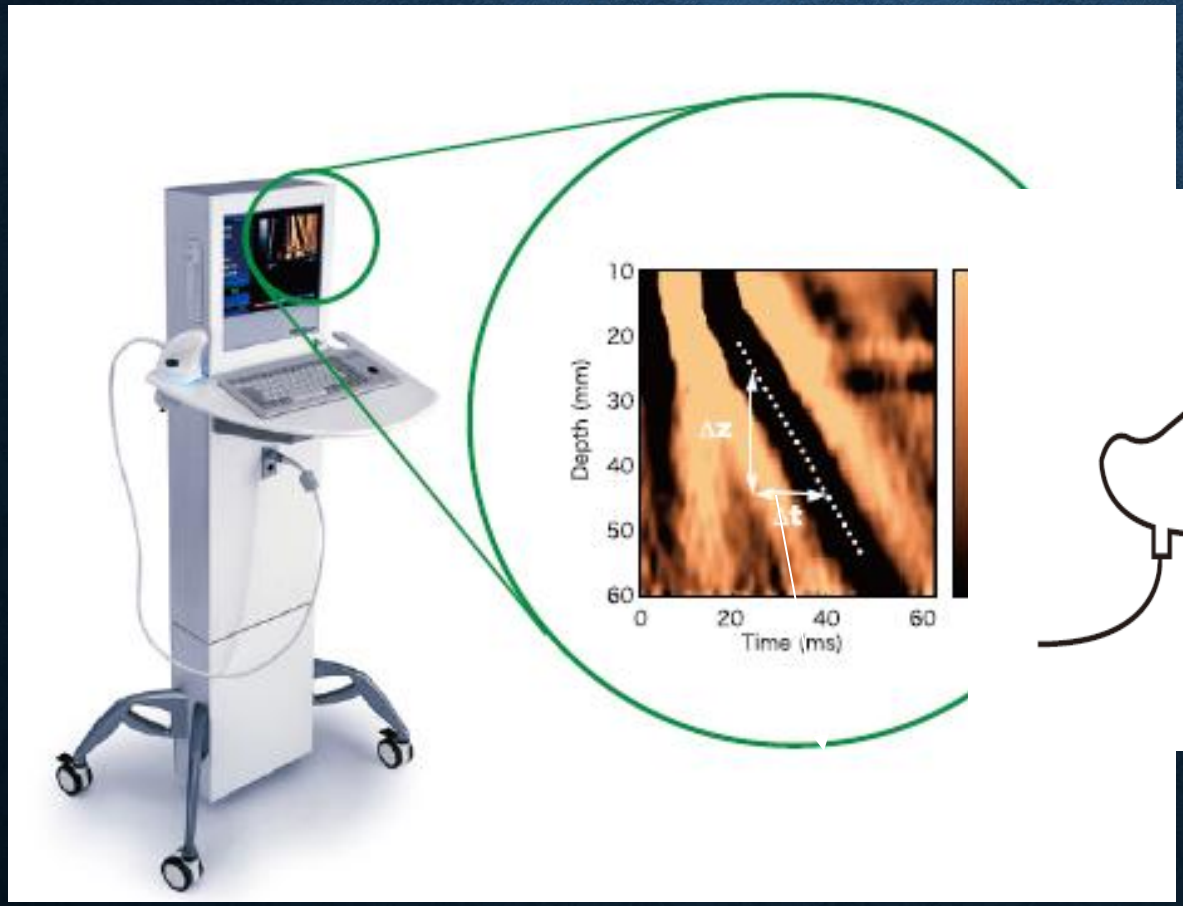
- **Disease stage can be assessed using vibration controlled transient elastography (VCTE),which is**

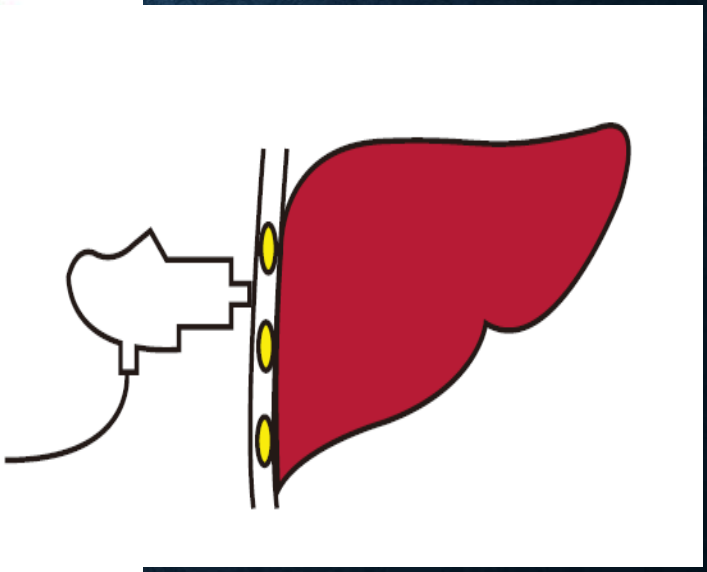
- **relatively *inexpensive* compared to magnetic resonance elastograstography (MRE)**

- **widely *available* at many academic medical centers**

# FIBROSCAN

- 3.5 MHz ultrasound transmitted from the vibrator toward the tissues
- pulse-echo ultrasound acquisitions are performed which is directly related to tissue stiffness.
- The harder the tissue, the faster the shear wave propagates
- The operator, assisted by ultrasound time-motion images
- liver portion at least 6 cm thick and free of large vascular structures
- The measurement depth is between 25 and 65 mm below the skin surface

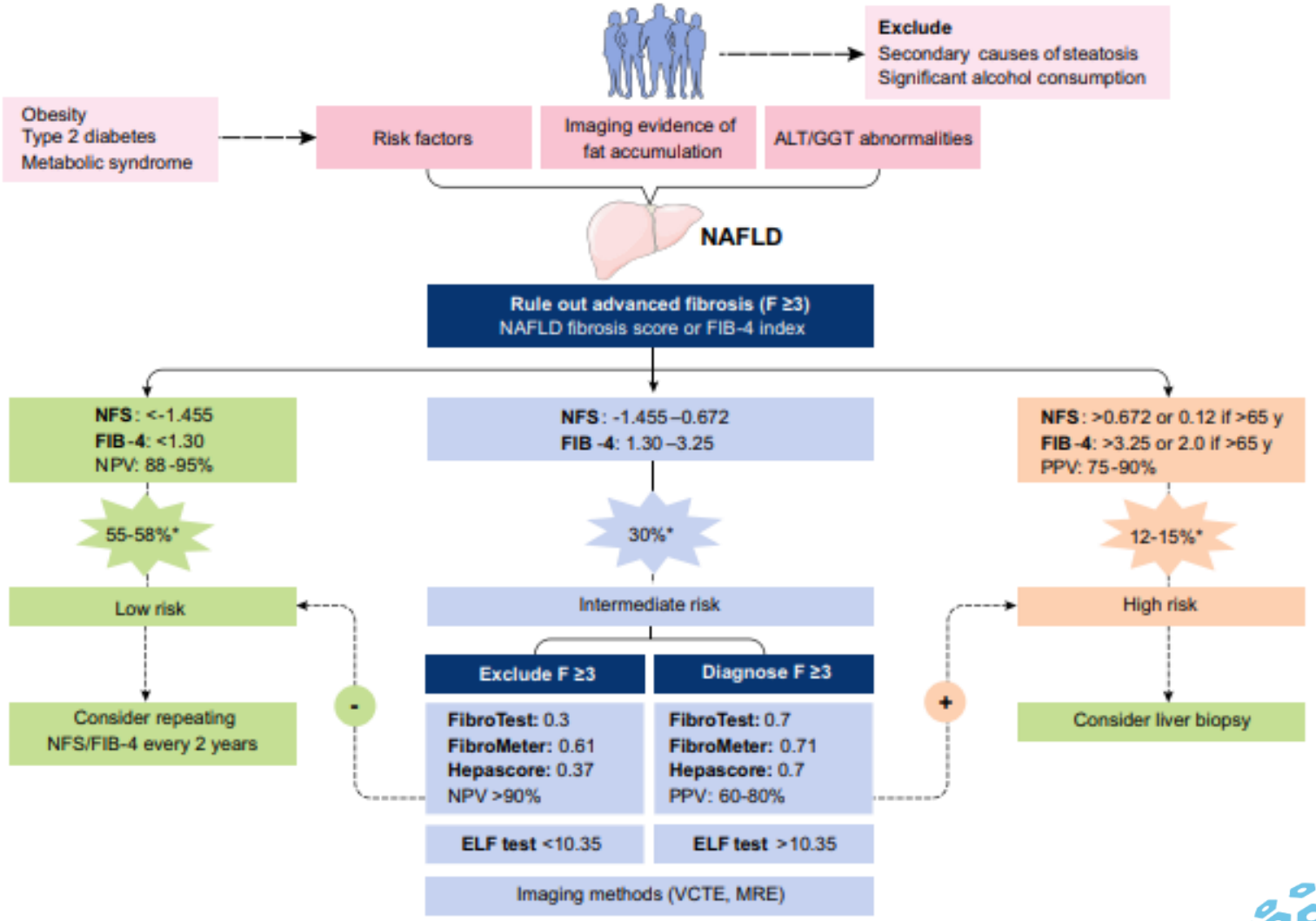


# ADVANTAGES

- *Safe*
- *Fast screening*
- *Acceptability by patients*
- *Longitudinal follow-up*
- *Efficacy of therapeutic treatments*
- *Prognostic evaluation*
- *Accurate*

# Potential algorithm for non-invasive assessment: prediction rules and blood-based biomarkers




*Estimated prevalence for low-, intermediate- and high-risk groups

Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15



EASL™ The Home of Hepatology

# MANAGEMENT OF PATIENTS WITH NAFLD

# WHOM TO TREAT?

***Pharmacological treatments*** **aimed primarily at improving liver disease should generally be limited to those with biopsy-proven *NASH and fibrosis*.**

# TREATMENT

- ***LIFESTYLE MODIFICATIONS*** INCLUDING :
  ***DIET***
  ***EXERCISE***
  ***WEIGHT LOSS***

REMAIN THE ***MOST EFFECTIVE*** THERAPY FOR (NAFLD).

WEIGHT LOSS OF ***3% TO 5%*** IS ASSOCIATED WITH DECREASED STEATOSIS

***7% TO 10%*** DECREASE IS NECESSARY TO ACHIEVE NAFLD/NONALCOHOLIC STEATOHEPATITIS REMISSION AND ***FIBROSIS REGRESSION.***

# COMPONENTS OF A LIFESTYLE APPROACH TO NAFLD

### *Energy restriction*
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

### *Fructose intake*
- Avoid fructose-containing food and drink

### Daily alcohol intake
- Strictly below 30 g men and 20 g women

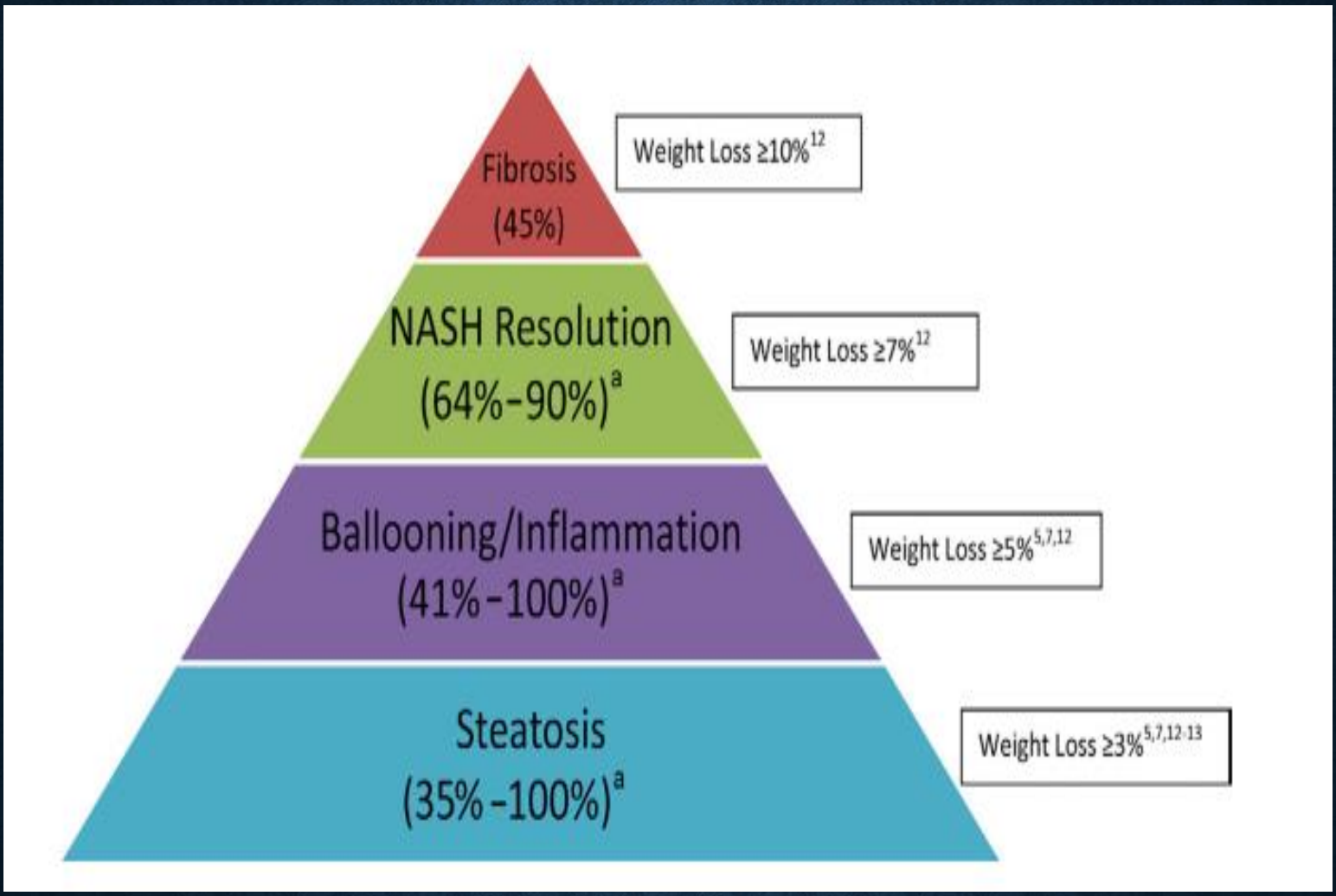
### *Coffee consumption*
- No liver-related limitations

**Comprehensive lifestyle approach**

### *Macronutrient composition*
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

### *Physical activity*
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402



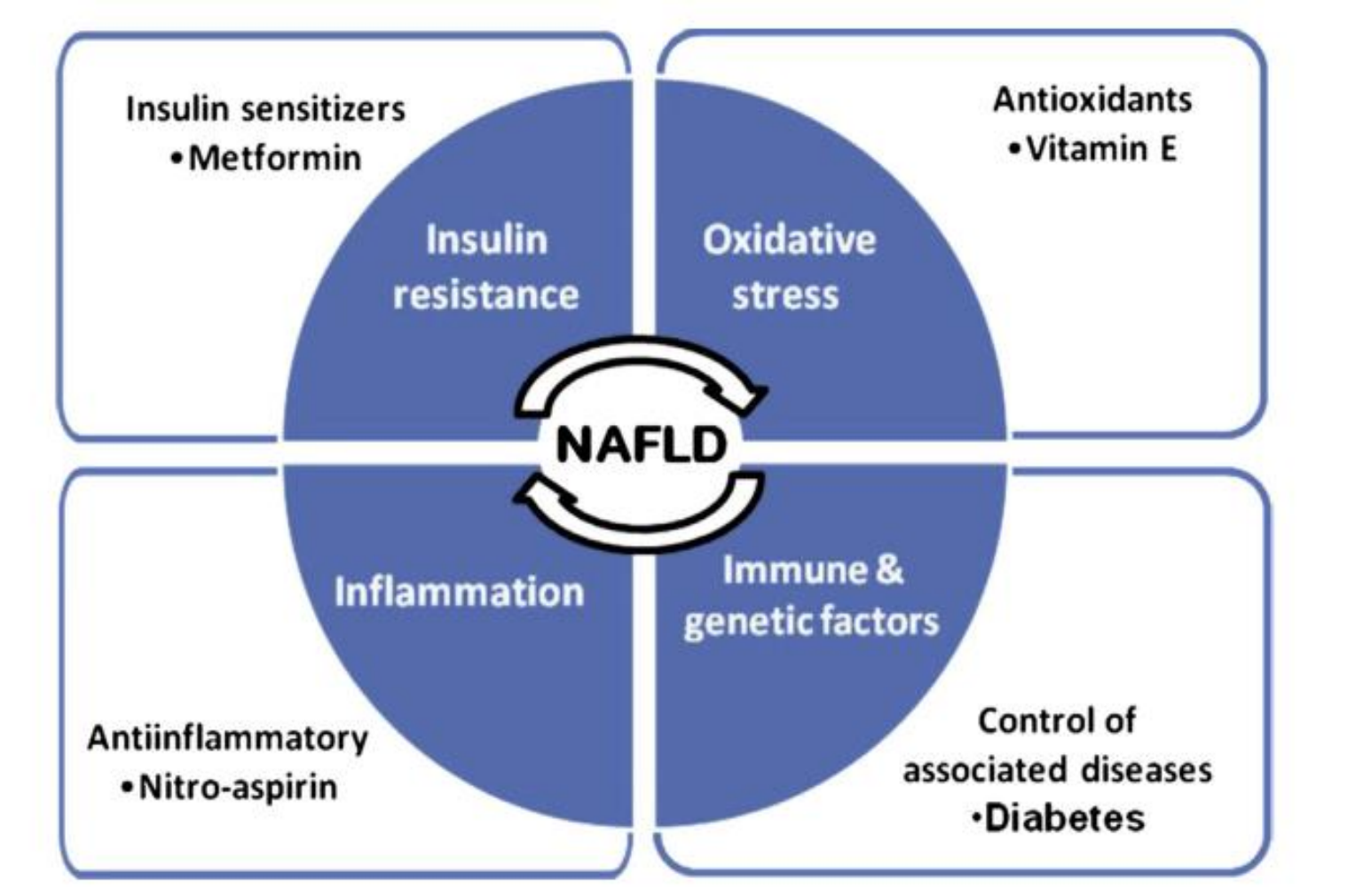

**Weight loss pyramid**

# TREATMENT

## *CURRENT PHARMACOLOGIC THERAPY*

- Modest but ***sustained weight loss***, ***regular exercise***, and ***diet*** composition modification seem to improve ***biochemical*** and ***histologic abnormalities.***

- Other therapies directed at ***insulin resistance***, ***oxidative stress***, ***cytoprotection***, and ***fibrosis*** may also offer benefits, but further studies are required.




Pathogenesis and potential therapy for NAFLD. Development of NAFLD is caused by interaction between multiple factors, mainly insulin resistance, oxidative stress, inflammation,and genetic predisposition. The potential therapies of NAFLD target one or more of these factors.

# INSULIN SENSITIZERS

## METFORMIN

several studies have shown an ***improvement*** in ***serum aminotransferases and IR***,

metformin ***does not*** significantly ***improve liver histology***.

Metformin is ***not recommended*** for treating NASH in ***adult patients***.

# INSULIN SENSITIZERS

## THIAZOLIDINEDIONES

**Pioglitazone improves *liver histology* in patients with and without T2DM with biopsy-proven NASH.**

**Until further data support its safety and efficacy, pioglitazone should *not be used* to treat NAFLD *without biopsy-proven NASH*.**

# VITAMIN E

**Vitamin E administered at a daily dose of 800 IU/day *improves liver histology* in *nondiabetic* adults with biopsy-proven NASH and therefore may be considered for this patient population.**

**Until further data supporting its effectiveness become available, vitamin E is**
*Not recommended* **to treat NASH in:**

- *Diabetic patients,*
- *NAFLD without liver biopsy,*
- *NASH cirrhosis,*
- *or cryptogenic cirrhosis*

# *BARIATRIC SURGERY*

**Foregut bariatric surgery can be considered in otherwise *eligible obese* individuals with *NAFLD* or *NASH.***

**The type, safety, and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with *established cirrhosis* attributed to *NAFLD* are not established.**

# *URSODEOXYCHOLIC ACID, OMEGA-3 FATTY ACIDS, AND MISCELLANEOUS AGENTS*

*UCDA* **is not recommended for the treatment of NAFLD or NASH.**

*Omega-3* **fatty acids should *not be used* as a specific treatmentof NAFLD or NASH,**
**but they *maybe considered* to treat *hypertriglyceridemia* in patients with NAFLD.**

# FARNESOID X RECEPTOR AGONISTS

- ***Farnesoid X*** (FXR) is the ***nuclear receptor*** for ***bile acids*** that play a ***critical role*** in:

- carbohydrate and lipid ***metabolism***
- and regulation of ***insulin sensitivity***

**Summary: pharmacologic therapies in the treatment of Non Alcoholic Steatohepatitis (NASH)**

| Treatment | Mechanism | Biochemical Effects | Histologic Effects | Comments |
|---|---|---|---|---|
| Orlistat | Weight loss | ↓ LFTs and insulin resistance | ↓ Steatosis, inflammation, NAS score | Improvement in inflammation and NAS seen if weight loss ≥9% |
| Rimonabant | Weight loss, possible peripheral effects | ↓ Insulin resistance, triglyceride levels, LFTs<br>↑ HDL and adiponectin levels | ↓ Steatosis | Animal data, psychiatric side effects |
| Incretin analogues (exendin-4) | Weight loss | ↓LFTs, insulin resistance, hemoglobin $A_1C$ levels | ↓ Steatosis | Animal and pilot studies in NAFLD; extensively studied in type 2 diabetes mellitus |
| TZDs | PPAR-γ agonists | ↓ LFTs, insulin resistance, and TNF-α levels<br>↑ Adiponectin levels | ↓ Steatosis, inflammation and fibrosis | Side effects: weight gain, peripheral edema, cardiac, fractures, need for maintenance therapy |
| Metformin | ↑ AMP kinase | ↓ LFTs and insulin resistance<br>No effect on adiponectin levels | +/– improvement in steatosis, inflammation, and fibrosis | Data conflicting; no RCTs |
| Vitamin E | ↓ Oxidative stress | ↓ LFTs | Uncertain | Large trials with histologic follow-up evaluation required |
| Betaine | ↓ Oxidative stress | ↓ LFTs | ↓ Steatosis, inflammation, fibrosis | Pilot study only |
| UDCA | Hepatoprotective | No change | No change | Not beneficial in large RCT |
| Pentoxifylline | Hepatoprotective | ↓ LFTs, TNF-α levels | ↓ Steatosis, inflammation | Pilot study only |
| HMG CoA-reductase inhibitors | Improve lipid panel | ? LFTs | Uncertain | Conflicting studies |
| Ezetimibe | Blocks cholesterol absorption in intestine | ? LFTs | ↓ Steatosis and fibrosis | Animal data |
| Angiotensin receptor blockers | ? Inhibits stellate cells | ↓ LFTs | ↓ Fibrosis | Animal and pilot studies |

# FOLLOW UP

Table **14** Follow-up tests and their timing

| Follow-up | Recommended |
|---|---|
| Evaluate weight loss, exercise, diet and lifestyle changes | After 6 months |
| Blood and platelet count | 2 × annually |
| Liver biochemical tests | 2 × annually |
| Prothrombin time | 2 × annually |
| Consult hepatologist | At 6 months and then yearly, depending on the response |
| Screening for cardiovascular risk | Every 1–2 years, depending on risk factors |
| Liver biopsy | Every 3–5 years, depending on response |
| Imaging tests | When indicated |