OVERVIEW AND MANAGEMENT OF NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN PRIMARY CARE

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NAFLD (INTRODUCTION)

- Epidemic of NAFLD is reshaping the field of hepatology.
- Increasing metabolic risk factors obesity, T2DM, dyslipidaemia and insulin resistance has lead to a parallel increase in NAFLD
- NAFLD is rapidly becoming the commonest cause of chronic liver disease in the west.
- Prompting the world wide societies to identify strategies to diagnose and treat NAFLD.

NAFLD (INTRODUCTION)

- NAFLD is a spectrum of disease from simple fatty liver to Non Alcoholic SteatoHepatitis (NASH) to cirrhosis
- The term NASH was first coined by Dr Jurgen Ludwig in 1987.
- Prevalence of NAFLD worldwide is between 10 to 25 % and growing. Rising to 90% in the morbidly obese.
- 23% prevalence of NAFLD in suburban Asian population in Malaysia.
- Prevalence of NASH is about 2-3 % of the general population and up to 37% in the morbidly obese.
- Bidirectional association between NAFLD and the metabolic syndrome.

NAFLD (INTRODUCTION)

- NAFLD has a strong association with type 2 Diabetes, with steatosis present in 70% of diabetics screened by ultrasound.
- NAFLD is becoming recognized as the hepatic manifestation of the metabolic syndrome.
- NAFLD is associated with increased mortality especially cardiovascular disease and liver related disease..
- In a recent US study NASH related cirrhosis was the fastest growing indication for liver transplantation.
- In the USA between 2000-2010 NASH associated HCC accounted for 34.8% of all HCC cases!!

NAFLD (DEFINITION)

- The characteristic points of NAFLD
  1. Evidence of excessive hepatic fat in the liver parenchyma (detected by imaging or histology)
  2. Absence of other secondary causes of hepatic fat deposition.
  3. Significant ongoing or recent alcohol consumption needs to be excluded (<20 gm/day in men and 10 gm/day in women)

METABOLIC SYNDROME

- Accumulation of several disorders which increases the risk of developing cardiovascular disorders, insulin resistance, diabetes and cerebrovascular disorders

- Metabolic disorders become a syndrome if patients have any 3 of the following:-
  1. Waist circumference >90 cm in men and >80 cm in women
  2. Elevated triglycerides >1.7 mmol/l or on treatment for high triglycerides
  3. Reduced HDL <1.3 in women and < 1.0 in men or on treatment
  4. Elevated fasting glucose >5.6 or on treatment for T2DM
  5. Blood pressure values >130 systolic, >85 diastolic or on treatment for hypertension

SECONDARY CAUSES OF FATTY LIVER

Excessive alcohol consumption

Drugs

- Estrogens
- Coumadin
- Tamoxifen
- Valproic acid
- Methotrexate
- Isoniazid
- Corticosteroids
- Vitamin A
- Troglitazone
- l-Asparaginase
- Amiodarone
- Perhexiline
- Calcium channel blockers
- Nucleoside analogues

Hepatitis C (genotype 3)

Nutritional factors

- Rapid weight loss
- Total parenteral nutrition
- Starvation
- Protein-calorie malnutrition

Surgical considerations

- Gastrointestinal surgery for obesity
- Extensive small-bowel resection

Metabolic disorders

- Cystic fibrosis
- Abetalipoproteinemia
- Others

Syndromes associated with obesity and insulin resistance

- Lipodystrophies
- Hypopituitarism
- Prader-Willi syndrome

NAFLD DEFINITION

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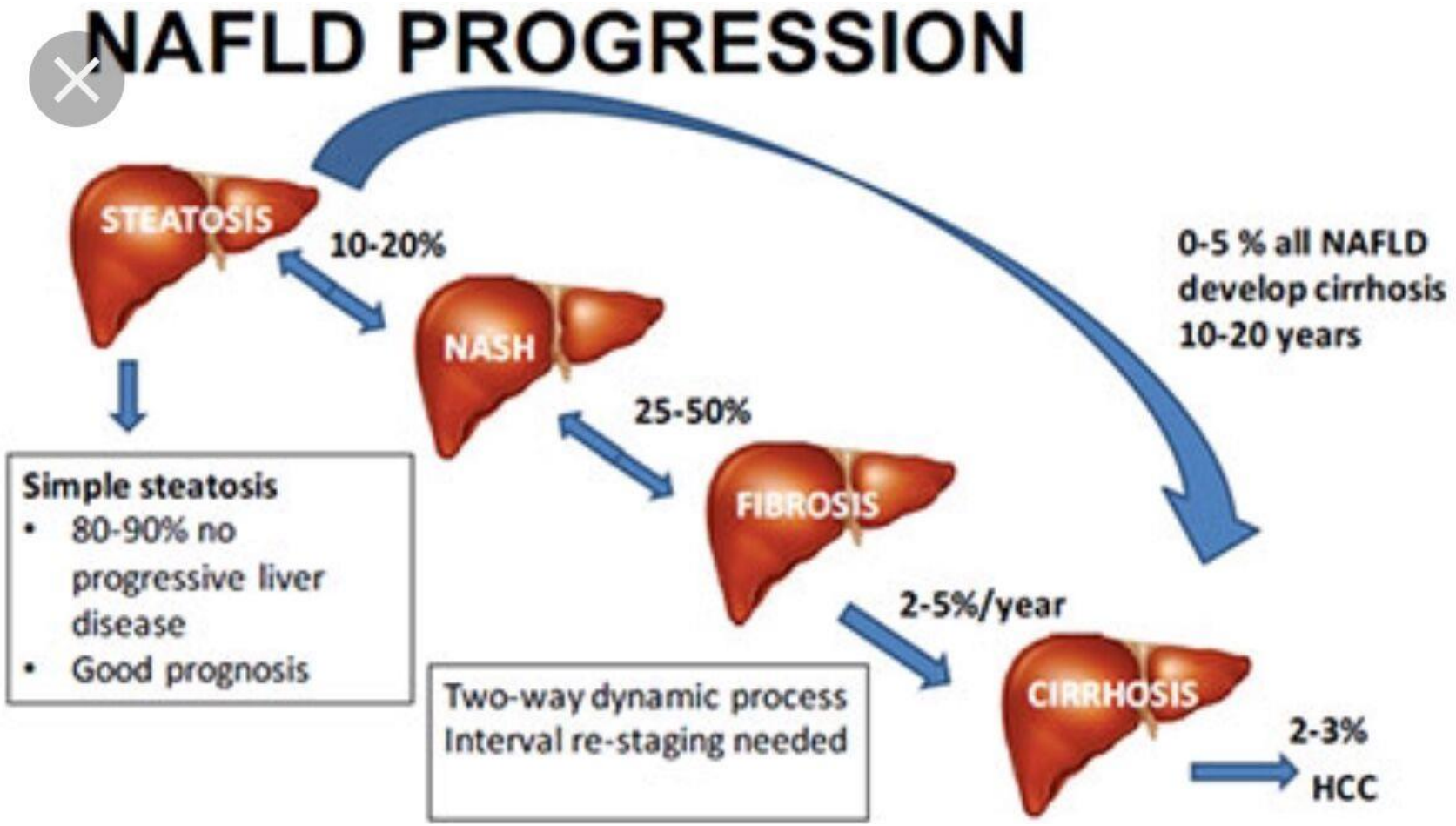
Table 1

Diagnostic criteria for non-alcoholic fatty liver disease according to the various guidelines

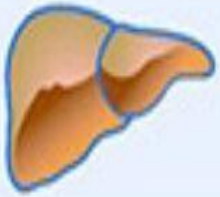
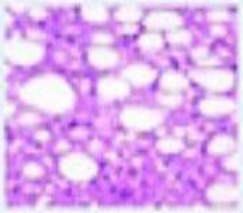
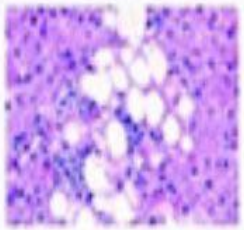
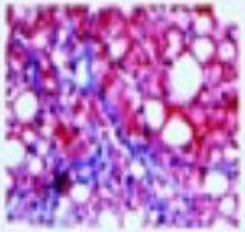
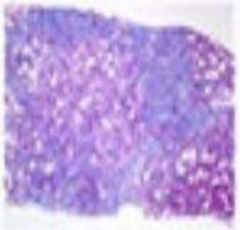
	EASL	NICE	Asia-Pacific	AISF	AASLD
Required criteria	Steatosis in > 5% of hepatocytes by either imaging or histology	Excessive fat in the liver	Hepatic steatosis by either imaging or histology	Hepatic steatosis on either imaging or histology	Evidence of hepatic steatosis either by imaging or histology
	No other causes of steatosis	No other causes of steatosis	No other causes of steatosis	No other causes of steatosis	No other causes of steatosis
	Insulin resistance	No significant alcohol consumption	No significant alcohol consumption	No significant alcohol consumption	No significant alcohol consumption
					No coexisting chronic liver disease
Alcohol consumption threshold (men)	30 g/d	30 g/d	2 standard drink/d 140 g/wk	30 g/d	21 standard drink/wk 294 g/wk
Alcohol consumption threshold (women)	20 g/d	20 g/d	1 standard drink/d 70 g/wk	20 g/d	14 standard drink/wk 196 g/wk

EASL: European Association for the Study of the Liver; NICE: National Institute for Health and Care Excellence; AISF: Italian Association for the study of the Liver; AASLD: American Association for the Study of Liver Diseases; MRI: Magnetic resonance imaging.

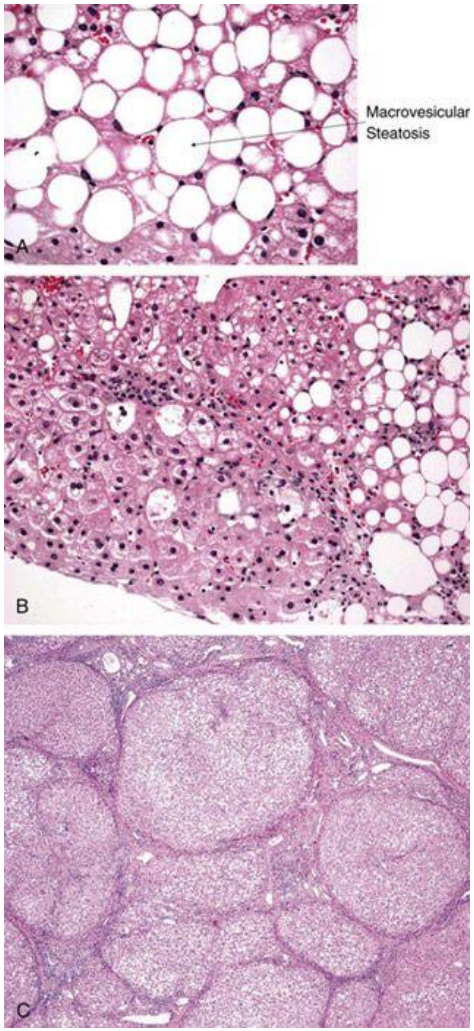
NAFLD PROGRESSION



NAFLD: Spectrum of disease

	Image	Histopathology	Pathophysiology
Non-alcoholic fatty liver (hepatic steatosis)			Accumulation of fat in liver (when excessive alcohol consumption is ruled out).*
Non-alcoholic steatohepatitis (NASH)			Accumulation of fat in liver is combined with inflammation and cell damage.
Fibrosis			Scarring (excess fibrous tissue) in an inflamed liver. Categorised into stages 0 to 4 (or mild, moderate and advanced) based on extent and distribution of scarring.
Cirrhosis			Late stage of chronic liver disease marked by nodules of damaged liver cells surrounded by scarring.

SPECTRUM OF NAFLD



NAFLD PATHOGENESIS

- Multifactorial and influenced by both environmental and genetic factors.
- Dysregulated lipid partitioning mediated by insulin resistance.
- Multihit hypothesis:-
  - 1ST HIT
    - **Imbalance of fatty acid metabolism** leading to **hepatic triglyceride accumulation**
    - A fatty liver makes it **susceptible to inflammation and fibrosis**
    - How does fat accumulate in the liver
      - 1)**lipolysis** of adipose tissue- triglycerides broken down to FFA and glycerol (60%)
      - 2) **denovo lipogenesis** (25%)
      - 3) **dietary intake** (15%)

NAFLD PATHOGENESIS(CONT)

- Multihit hypothesis:-
  - 2nd hit
    - **Inflammatory cytokines** (TNF and interleukins)
    - **Adipokines**
      - Adipose derived cytokines (leptins and adiponectins)
      - Leptins produced by adipose tissue
        - Regulate energy intake and expenditure, regulate the immune system and **promotes inflammation**
        - **High levels** seen **in obese and those with NAFLD**
      - Adinopectins
        - **Levels reduced in the obese and in NAFLD**
        - **Anti-inflammatory** and increases insulin sensitivity
    - **Oxidative stress and mitochondrial dysfunction**
      - Beta oxidation occurs in the mitochondrum
      - **helps reduce FFA in the liver**
      - In NAFLD this process is **overwhelmed** and results **in mitochondrial dysfunction** and this increases inflammation

NAFLD (PATHOGENESIS)

- Multihit hypothesis :-
  - 3rd hit
    - **Faulty apoptosis**
      - In healthy liver cell deaths leads to replication of new hepatocytes
      - In NAFLD with oxidative stress this process is inhibited
      - Instead progenitor/oval cells are produced (**hepatocyte like**)
      - This progenitor cells have been **impicated in HCC carcinigenesis**

NAFLD (PATHOGENESIS)

- INSULIN resistance
  - Insulin help to **prevent lipolysis** and helps in **beta oxidation of FFA** in the liver and **reduces denovo lipogenesis**
  - In states of **insulin resistance, the opposite occurs**, resulting in **FFA accumulation** and **increased liver inflammation**

- FFA
  - In the normal liver FFA is reesterified to Triglycerides, betaoxidation occurs and some are packed into VLDL and transported out of the liver
  - In NAFLD , FFA accumulation **results in oxidative stress** and activates inflammatory pathways.

NAFLD PATHOGENESIS(CONT)

- Genetics
  - Prevalence of NAFLD is 10-25 %.
  - Steatosis is common in the obese and those with IR
  - But only a small proportion actually develop NASH
  - **Polymorphism in genes related to lipid metabolism**, IR, oxidative stress, cytokines and adipokines may all increase susceptibility to NASH development
  - **Single neuclotide polymorphism** (SNP) have been demonstrated in angiotensinogen and TGF Beta 1 genes which results in increased NAFLD fibrosis.

NAFLD PRESENTATION

- Asymptomatic with normal blood tests and investigations. (need to be suspicious, more so in the presence of the metabolic syndrome)
- Incidental elevations of liver enzymes.
- Routine ultra sound abdomen showing fatty liver(U/S has a sensitivity of 50-90 % but specificity of about 80%)
- Patients with cirrhosis may present with evidence of chronic liver disease and complications of portal hypertension,
- Most patients have associated features of the metabolic syndrome.

SO WHAT NEXT?

- HISTORY
  - Metabolic syndrome (diabetes, hyperlipidaemia, hypertension)
  - Alcohol quantify
  - Medication history
  - Blood transfusion, history of tattoos, high risk behaviour, hepatitis B, Hepatitis C history
  - History of jaundice and family history of liver related disorders.

SO WHAT NEXT

- PHYSICAL EXAMINATION
  - Blood pressure
  - Weight and waist circumference
  - Evidence of chronic liver disease and complications of portal hypertension
    - Jaundice
    - Spider naevi, palmar erythema
    - Splenomegaly. Hepatomegaly, ascites

NAFLD (BLOOD INVESTIGATIONS)

- Blood investigations
  - Liver functions
    - Can be normal- does not exclude NAFLD . ALTs do not predict fibrosis.
    - Mild elevations in ALT, AST,GGT (usually not more than 5 times upper limit of normal.
    - AST to ALT ratio less than 1
  - Fasting lipids and Fasting glucose levels
  - Viral serology
    - Hep b s ag and hep C Ab
  - Autoimmune screening
    - Antinuclear ab, antismooth muscle ab
  - Metabolic tests
    - Ferritin and serum ceruloplasmin

NAFLD (IMAGING)

- Ultasound
  - 1st line examination , broadly available and low cost
  - Useful for confirming steatosis (needs 20-30 % of hepatocytes to contain fat droplets)
  - Sensitivity of between 50-90% and specificity 80%
  - Sensitivity low in morbidly obese patients -50%
  - Cannot differentiate simple steatosis from NASH /operator dependent/ cannot quantify fat content/not useful for fibrosis assessment

ASSESSMENT FOR LIVER FIBROSIS

- **Non invasive** tests are needed.
- Liver **fibrosis most important prognostic** factor in NAFLD.
- Liver **fibrosis** relates to liver related **complications and mortality**.
- **Closer monitoring** required in more **advanced fibrosis**

TESTS/SCORES TO ASSESS LIVER INFLAMMATION/FIBROSIS

- Need for **non invasive tests** to assess fibrosis that are **reliable , reproducible, easy to perform and inexpensive**.
- **Optimal tests** should not only be effective for **staging** but also for **monitoring disease progression** and **response to treatment.**

TESTS/SCORES TO ASSESS LIVER INFLAMMATION/FIBROSIS (cont)

- 3 tests which stand out are
  - **Vibration controlled Transient Elastography**
  - **FIB 4**
  - **NAFLD /FATTY LIVER fibrosis scores**
- These tests have been validated in various studies predicting CVS and liver related mortality.
- They also have the best predictive value for advanced fibrosis

NAFLD (IMAGING CONT)

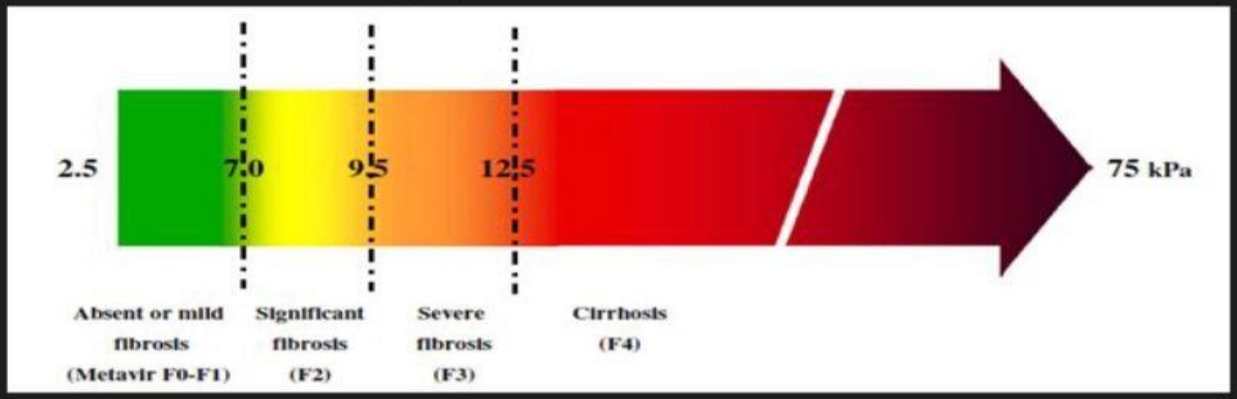
- **Ultrasonography based transient elastography**
  - Ultra sound **probe mounted on the axis of a vibrator**. U/S probe has a **transducer which measures the speed of waves** created by the vibrator
  - **Speed of these waves** correlates with the **stiffness of the tissue**.
  - Waves travel **faster through denser tissues**
  - Test is **reproducible**, allows **staging of liver fibrosis**
  - Not so good to differentiate mild and moderate fibrosis, **limitation in the obese and patients with ascites**
  - **Useful to monitor** regression and progression with treatment

NAFLD (IMAGING CONT)

TRANSIENT ELASTOGRAPHY (FibroScan)

- Results are expressed in kPa and correspond to the median of **10 validated measurements. Liver stiffness values range from 2.5 to 75 kPa.**
- Use of **ranges of values** rather than a single cut-off value

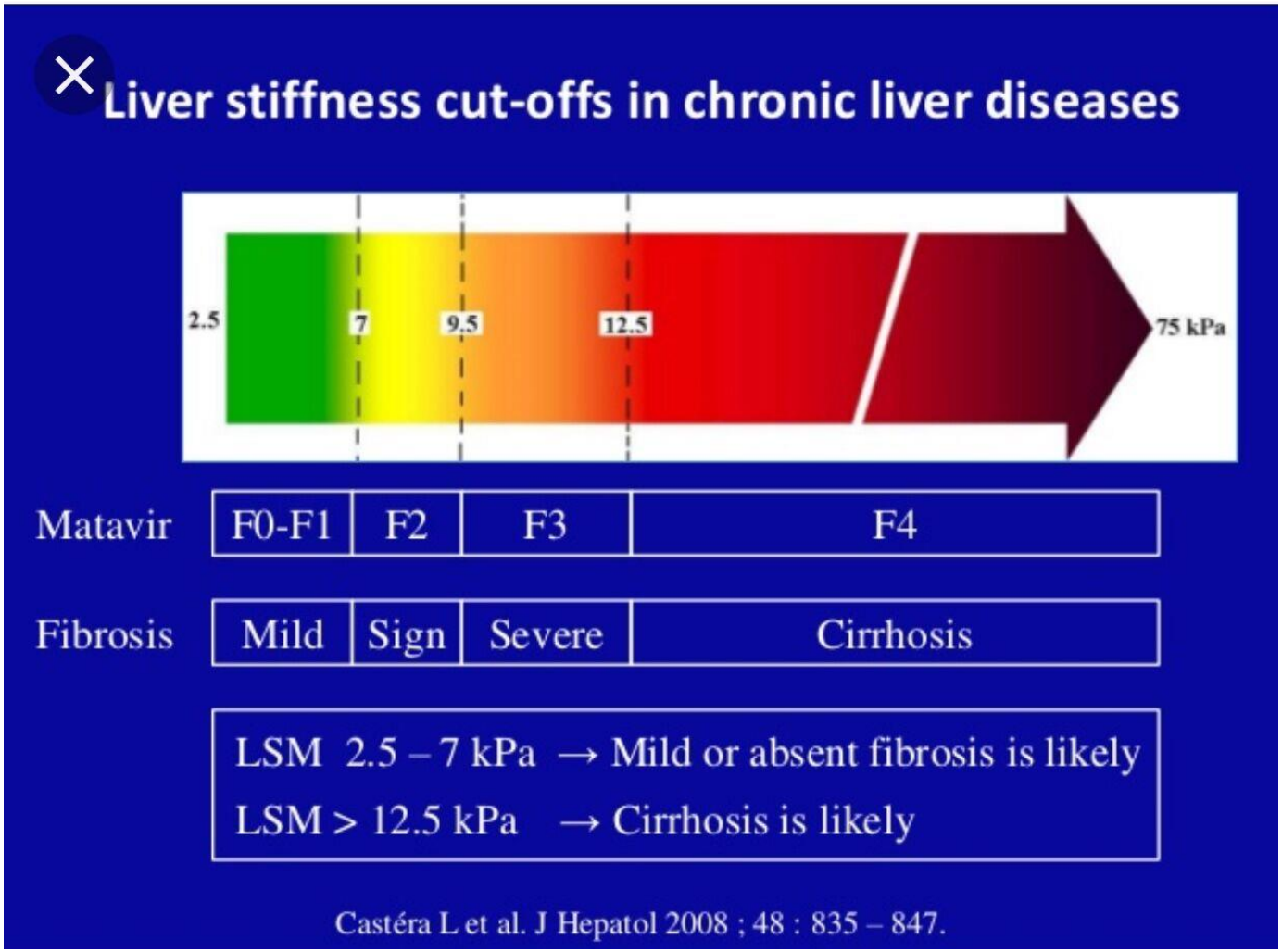
Combining TE results with serum markers increases diagnostic accuracy and liver biopsy can be avoided.



Limitations:

- Failure in ≈5% of cases, mainly in **obese** patients (BMI > 29) or in those with narrow intercostal space
- Not feasible in patients with ascites

NAFLD (IMAGING CONT)



NAFLD (IMAGING CONT)

- **Ultrasonography based continuous attenuation parameter(CAP, steatosis measurement)**
  - A transducer on the u/s probe measures the amplitude of the wave as it travels through the liver
  - This translates to measurement of the amount of fat in the liver ie steatosis

FIB 4 score

- This score comprises data including **age, AST, ALT and platelet counts.**
- FIB 4, score of >2.67 had an 80% positive predictive value for advanced fibrosis and a score of < 1.3 had a 90% negative predictive value of advanced fibrosis. A score of 1.43 predicted stage 1 fibrosis or higher.

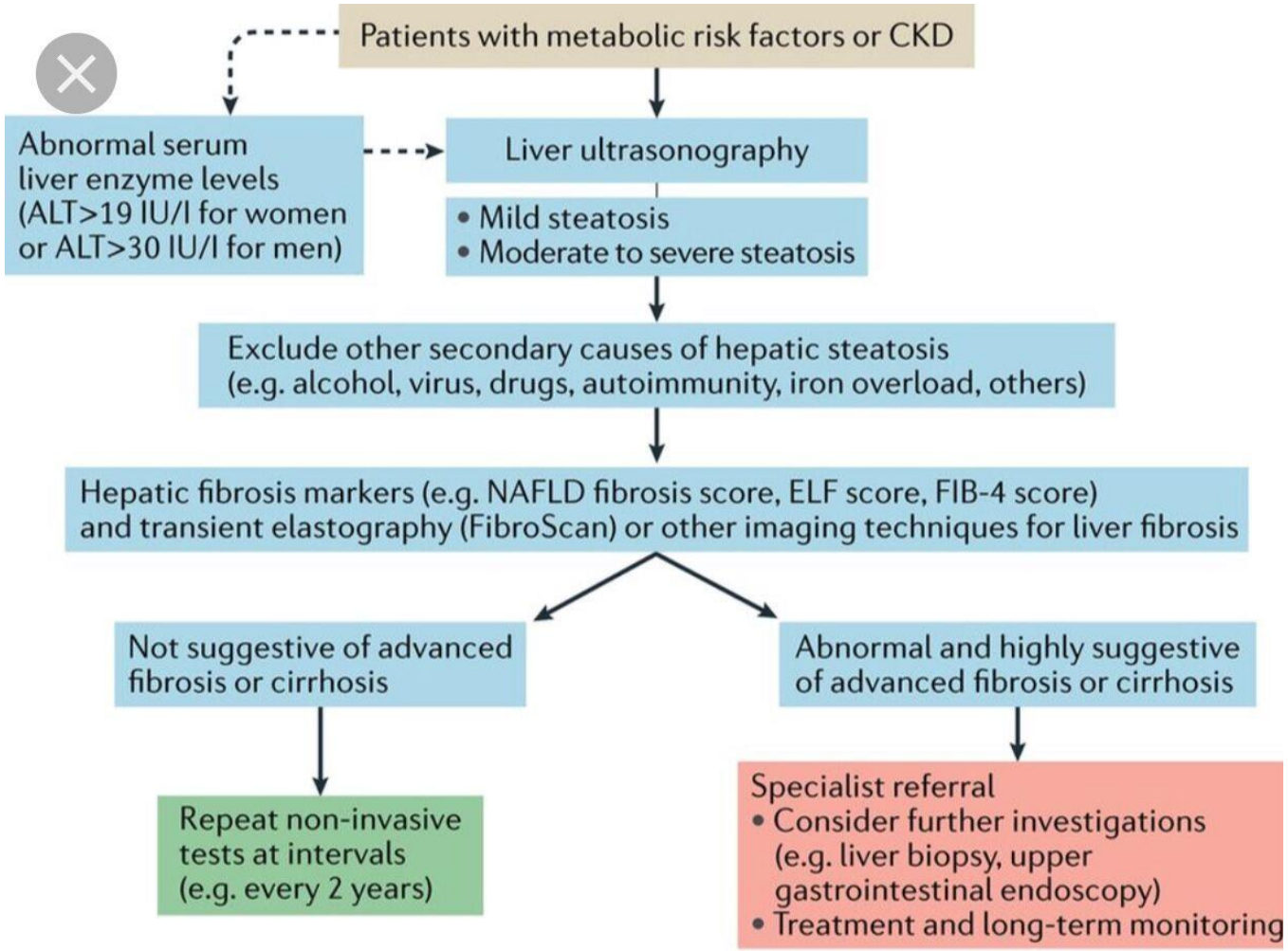
NAFLD/FATTY LIVER FIBROSIS SCORE (NFS)

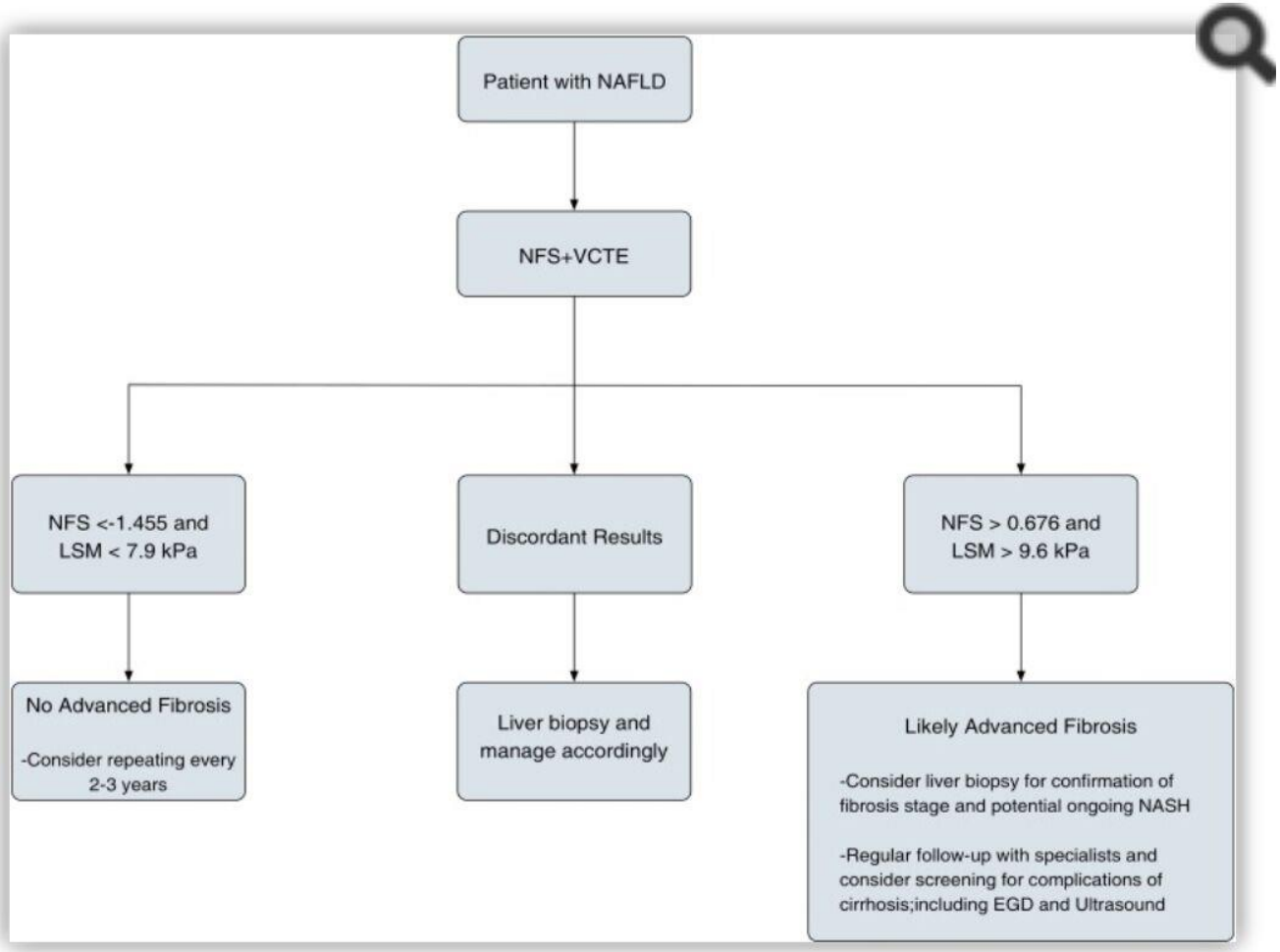
- One of the **most studied** scoring systems.
- **Recommended by AASLD and EASL** in the assessment of patients for advanced fibrosis.
- **6 variables** utilized, age, hyperglycaemia, BMI, platelet count, albumin and AST/ALT ratios
- Score of **< -1.455** had 90% sensitivity and 60% specificity in **excluding advanced fibrosis** .
- Score **>0.67** had 67% sensitivity and 97% specificity in **identifying advanced fibrosis** and also for identifying all cause mortality

Liver biopsy

- Remains the gold standard for diagnosing NASH (hepatocyte ballooning and lobular inflammation) and staging liver fibrosis.
- Findings on liver biopsy
  - (stages of fibrosis)
    - Perisinusoidal fibrosis, portal fibrosis, bridging necrosis finally cirrhosis
  - Degree of steatosis
  - Degree of inflammation
- Limitations
  - Sampling error (2 cm core , 1:50000 fraction)
  - Variability in pathologists interpretation
  - Cost
  - Patient discomfort
  - Procedural risk
    - Bleeding, visceral injury and death.
- Reserved for those with uncertain diagnosis and suspect NAFLD with advanced liver disease.(mainly for prognostication)
- Not recommended in all cases of NAFLD

MANAGEMENT ALGORITHM





Proposed algorithm for assessing NAFLD patients for advanced fibrosis.

NAFLD TREATMENT

- **Treatment is 2 pronged**
  - Treatment of **metabolic comorbidities**
    - Insulin resistance
    - Obesity
    - Hyperlipidaemia
    - Type 2 diabetes
  - Treatment of **liver disease**(mainly NAFLD with inflammation/fibrosis)

Treatment of liver Related inflammation/fibrosis

- **Lifestyle intervention**
  - Diet/weight loss
  - Exercise
- **Medications**
  - Thiazolidinediones
  - GLP1 Agonists (glucagon like peptide)
  - Vitamin E
  - Silymarin
  - Statins
- **Bariatric surgery**
- **Liver transplantation**

Lifestyle Intervention

- Consists of diet, exercise and weight loss
- Weight loss is the key stone element
- Guidelines recommend dietary restrictions of 500-1000kcal/day; weight loss of 500-1000gm a week. 7-10% total body weight loss.
  - 5% weight loss reduces steatosis
  - 7%weight loss reduces steatosis/hepatitis
- Physical activity
  - aerobic activity of 150 minutes a week
  - At least 6 METS (metabolic equivalent) for reduction in steatosis, 10 METS to reduce fibrosis
- No real specific suggestions on type of diet recommended.(low to moderate fat, moderate to high carbohydrate, keto diet with low carbs)

MEDICATIONS

- Generally medications recommended
  - for biopsy proven NASH.
  - Bridging fibrosis (advanced fibrosis) and cirrhosis
  - Early stage NASH with high risk of disease progression
    - Age >50, metabolic syndrome, diabetics and those with elevated ALT
- Medications not recommended for those with plain steatosis

MEDICATIONS (cont)

- Thiazolidinediones
  - Pioglitazone 30-60 mg
  - Has effects on lipid and glucose metabolism
  - Reduces adipose tissue dysfunction and reduces insulin resistance
  - Reduces AST, steatosis and inflammation.
  - Useful in both biopsy proven NASH both in diabetics and non diabetics
  - Side effects include weight gain
  - Guidelines allow their use in biopsy proven NASH and in diabetics with NAFLD.

Medications (cont)

- **Vitamin E**
  - Antioxidants, counters the effects of oxidative stress .
  - Reduces steatosis and inflammation.
  - Recommended for patients with biopsy proven NASH
  - 400-800 IU daily
  - **AASLD recommend its use** in biopsy proven NASH
  - EASL wants more studies and APASLD feels it is non beneficial.

Medications(cont)

- **GLP (Glucagon- like peptide)-1 Agonists**
  - Incretomimetics
    - Increase insulin, reduces glucagon, increases satiety, reduces weight
    - Given subcutaneously daily/weekly
    - Reduces steatosis, inflammation and has effect on fibrosis.
    - Associations recommend more studies.
    - But in **Diabetics with NAFLD this is definitely something to consider**.

Medications (cont)

- Silymarine
  - is a mixture of 6 major flavonolignan obtained from plants .
  - **Randomised controlled trials shows usefulness in biopsy proven NASH to reduce inflammation and fibrosis**
  - **Asia Pacific guidelines mentioned its potential usefulness in treatment of biopsy proven NASH.**
  - **Dose of 700 mg 3 times daily**

Medications (cont)

- Statins
  - **Safe to use in NAFLD** , more so in patients with associated cardiovascular risk.
  - Safe to use even in **compensated cirrhosis**
  - Safe to use in patients with ALT up to 3 times upper limit of normal.
  - **Avoid in acute liver failure and decompensated cirrhosis.**

Bariatric surgery

- In **those unresponsive to lifestyle changes and pharmacotherapy.**
- An option for weight reduction and reducing metabolic complications. (reduces comorbid diseases and reduces mortality from cardiovascular disease)
- **Improves liver histology (improvement seen within 1 year)**
- **Asia pacific guidelines recommends Bariatric surgery in those with grade 2(severe obesity) and above (35kg/m2) and above.**

LIVER TRANSPLANTATION

- **NASH is becoming the most common indication for liver transplantation in the west.**
- Because of the associated comorbidities in NASH ie obesity, cardiovascular and chronic kidney disease , there is a **higher risk** of post transplant complications and graft loss.
- Most of the **guidelines agree that liver transplant is acceptable in NASH patients with end stage liver disease**.

SUMMARY

- NAFLD prevalence is continuing to increase
- Closely associated with the metabolic syndrome.
- Should be suspected even in those with normal liver functions.
- Use of non invasive tests to identify those with significant fibrosis in the primary care.
- In primary care , lifestyle modifications and management of comorbidities is the cornerstone of treatment.
- No specific medications available.
- Referral for specialist management when fibrosis or cirrhosis is suspected.
- In the near future NAFLD is projected to become the commonest cause of chronic liver disease and HCC and number one indication for liver transplantation.

THANK YOU