Fatty Liver
(The slides have been changed)

No.26

Editing file

Objectives :

- ★ Nomenclature /definition
- ★ Epidemiology
- ★ Pathophysiology
- ★ Diagnosis
- ★ Treatment

Doctor's notes are extremely important!

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Text book
Important
Golden notes
Extra

Fatty liver

◀ Definition

- **NAFLD** "nonalcoholic fatty liver disease (**old name**)" is defined by **≥5%** of hepatocytes display **macrovesicular steatosis** (differs from microvesicular steatosis) in the absence of a readily identified alternative cause of steatosis (eg, medications, starvation, monogenic disorders) in individuals who drink little or no alcohol.
  (Note that fatty liver and alcoholic fatty liver have **macro**vesicular steatosis)

- **NASH** "nonalcoholic steatohepatitis" is additionally characterized by the **presence of inflammation** and cellular injury (**ballooning**), with or without fibrosis, and finally cirrhosis, which is characterized by bands of fibrous septa leading to the formation of cirrhotic nodules (It is important to differentiate between NAFLD and NASH)
  NASH is characterized by ballooning, inflammation and **Mallory-Denk Bodies**.

- Multinational Liver Societies Announce New "Fatty" Liver Disease Nomenclature That Is Affirmative And Non-Stigmatizing. June 24,2023 (They changed the name because they think that "fatty liver" is stigmatizing. Fatty liver disease became —> Steatotic liver disease)

◀ What's New?

- Steatotic liver disease (**SLD**) was chosen as an **overarching** term to encompass the various aetiologies of steatosis. (Every term below **is a part of SLD**. Check the next slide)

- NAFLD will now be metabolic dysfunction-associated steatotic liver disease (**MASLD**). MASLD encompasses patients who have **hepatic steatosis** AND have at least **one of five cardiometabolic risk factors**. NAFLD has changed to MASLD.
  MASLD Diagnosis = hepatic steatosis + at least ONE of five cardiometabolic risk factors.

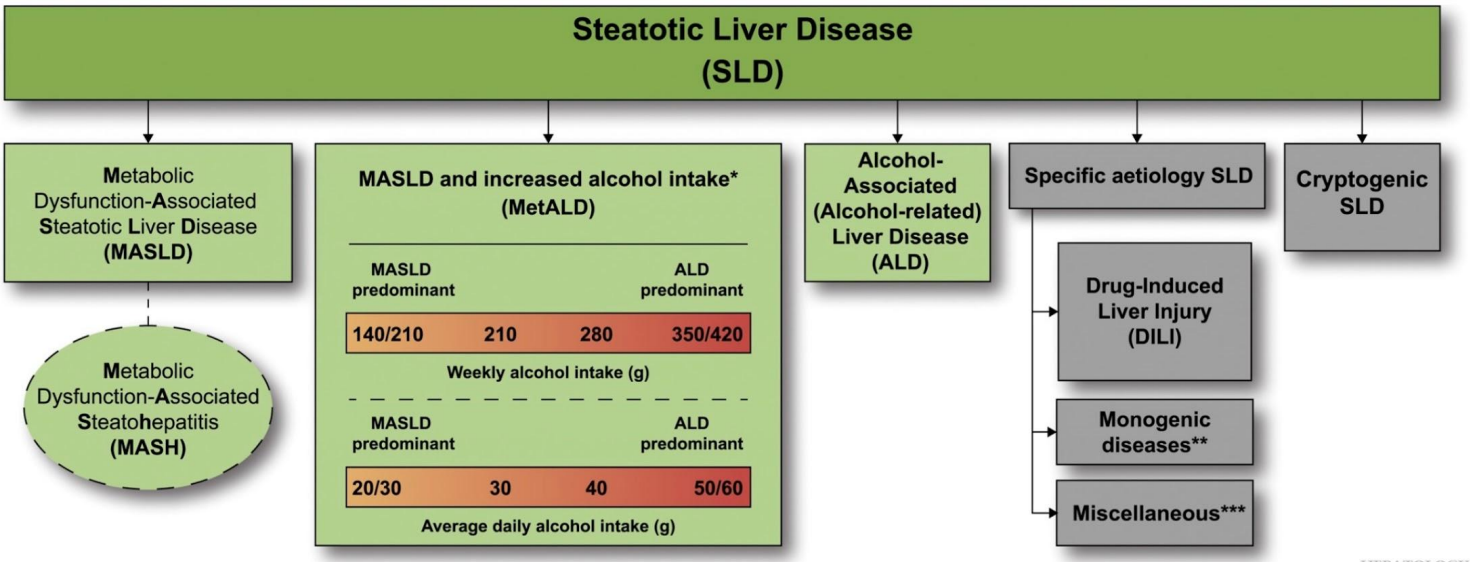
- **MetALD** describes those with MASLD who consume greater amounts of alcohol per week (140 g/week and 210 g/week for females and males respectively).

- Metabolic dysfunction-associated steatohepatitis (**MASH**) is the replacement term for NASH. NASH has changed to MASH. In the past, you can't diagnose the liver with NASH or fatty liver disease unless you take a **biopsy**. You need a biopsy for the diagnosis!. Nowadays, you can diagnose fatty liver with **radiological studies** but if there is inflammation (NASH) **then you need a biopsy**. You can't tell if there is inflammation by only radiological studies. You must have a biopsy.

- Those with no metabolic parameters and no known cause have **cryptogenic SLD**.
  Cryptogenic SLD: There is only macrovesicular steatosis due to unknown cause, the patient has no cardiometabolic risk factors.

Fatty Liver

◀ Steatotic Liver Disease Classifications



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
e.g. **Lysosomal Acid Lipase Deficiency (LALD), **Wilson disease**, **hypobetalipoproteinemia**, **inborn errors of metabolism**
***e.g. **Hepatitis C virus** (HCV), **malnutrition**, **celiac disease**

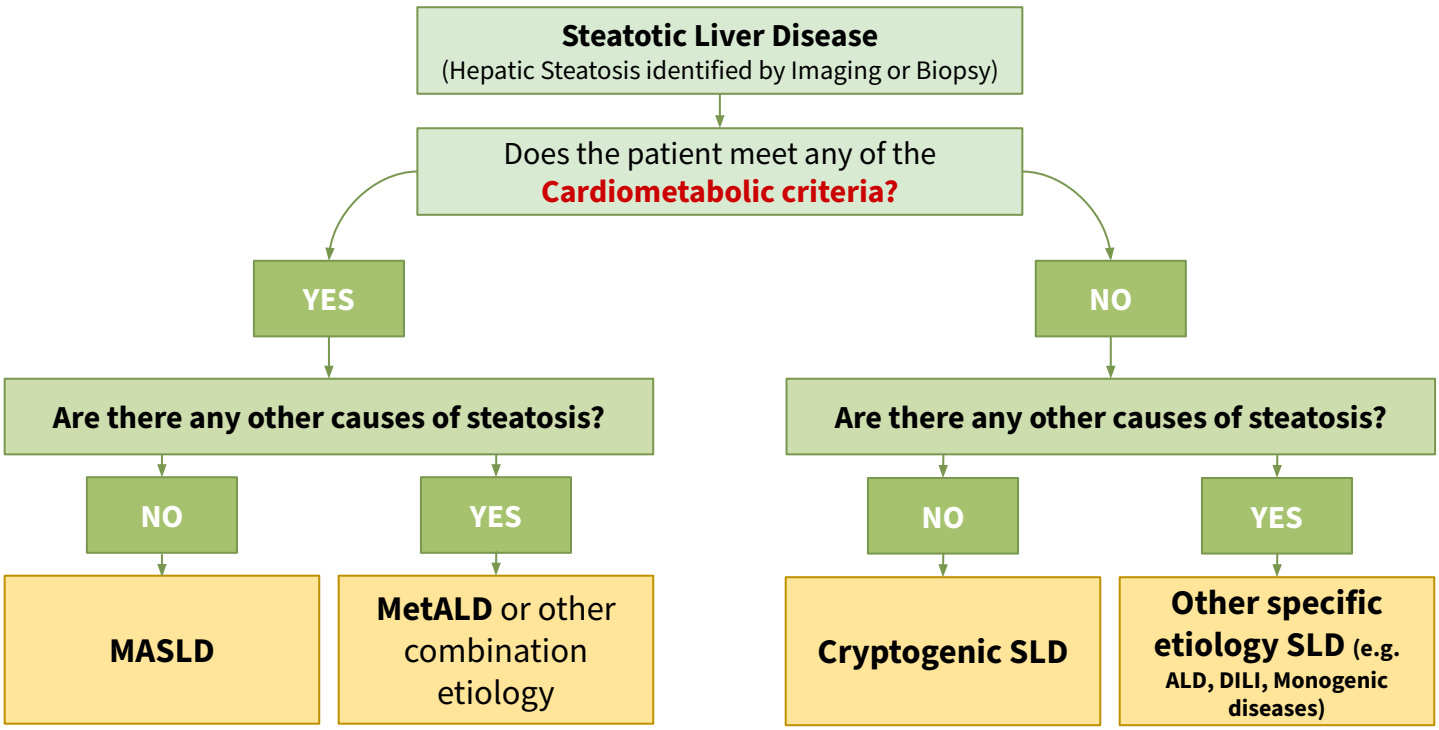
◀ MASLD Diagnostic Criteria

HOW to diagnose MASLD?

1. Radiological or Histological (Biopsy) Evidence

PLUS

2. One of the five cardiometabolic risk factors (next slide)



- NAFLD is overarching "يسمل" for all liver disease, NASH comes below NAFLD with element of inflammation
- MetALD it is combination MASLD and ALD, depend on alcohol consumption. But there is no histological difference
- MASH is Below MASLD
- Both NAFLD and NASH are defined by **histology**
- Other sub-classification for SLD: Alcoholic (ALD) and Specific aetiology SLD
- Old terms: NAFLD & NASH. New terms: MASLD & MASH, SLD encompasses all terms.

Fatty liver

◀ MASLD Diagnostic Criteria

It is important to know the five cardiometabolic risk factors of adults criteria
Doctor said that it is not important to know the pediatric criteria. He skipped it :)

***Cardiometabolic criteria**

Adult Criteria (Important)	Paediatric Criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted equivalent
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment	☐ Plasma triglycerides age < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

1- In the presence of hepatic steatosis, the finding of any of a cardiometabolic risk factor, would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis.
2- If additional drivers of steatosis are identified. then this is consistent with a combination etiology. In the case of alcohol this is termed MetALD.
3- In the absence of overt cardiometabolic criteria, other etiologies must be excluded and if none is identified, , this is termed cryptogenic SLD, although depending on clinical judgment could also be deemed to be possible MASLD and thus would benefit from periodic reassessment on a case-by- case basis
Reference

- In the past, without taking liver biopsy, doctors couldn't know whether it is NASH or NAFLD so if they didn't take biopsy they will call it cryptogenic. But now, you can know fatty liver by radiological studies without the need of biopsy.
- **Important!** How can you know if the patient has Fatty liver disease? two parameters:
  1-Fatty liver disease is known by radiological studies "liver is steatotic in imaging. US, CT, MRI or fibroscan" **or histological** "macrovesicular" **and this is not enough alone**.
  2- You need at least one cardiometabolic risk factors.
- What's imp is radiological, histological and the risk factors.
- In radiological studies , you will find steatotic liver but you can't know whether it is macrovascular or microvascular (you can know it only by histology- biopsy)
- **You might be asked: What are the cardiometabolic risk factors for the presence of hepatic steatosis? You should know at least one of the 5 factors of adult criteria.**

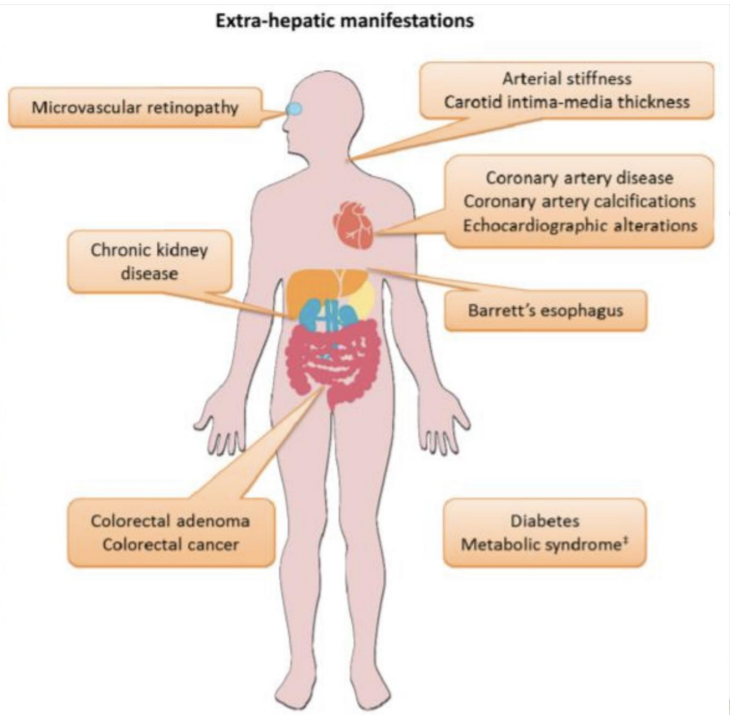
Fatty liver

◀ SLD/MASLD Impact

- Estimated to have a global prevalence of 25%.
- Rise paralleled to the rise of **metabolic syndrome** (HTN, Obesity and specially Diabetes)
- NASH is two-fold higher in patients with **T2DM**. Imp risk factor.
  If the patient has or suspected to have NASH based on cardiometabolic risk factors. He/she should be **screened for Type 2 diabetes.**
  (Everyone who has NASH/Suspected NASH → should be screened for **T2DM**)
- **Age** is a risk factor with highest prevalence in ages 70-79. (The chances of having fatty liver increases with age)
- The Middle East has the highest prevalence of MASLD (31.8%)
- **Complications:** In addition to **cirrhosis** and **HCC** , MASLD increases the incidence of **CVD** (most common cause of death) , **T2DM**, **CKD** and **extrahepatic cancers**.
- Estimated direct cost of medical care of $100 billion annually in the US.

◀ Risk factors and Extra-hepatic manifestations

Risk factors
1. Increased age
2. Male gender
3. Certain ethnicities (Indian, Malay)
4. Genetic variants (PNPLA3)
5. **Diabetes mellitus**
6. **Insulin resistance**
7. **Obesity (increased body-mass index)**
8. **Central obesity (increased waist circumference)**
9. **Metabolic syndrome**
10. Unhealthy dietary patterns
11. Physical inactivity
12. Low vitamin D levels
13. Hypothyroidism
14. Obstructive sleep apnea
15. Tamoxifen (Team439)



Important: You should know the factors that are associated with fatty liver disease .

Fatty liver

◀ Pathogenesis[1]

- Determined by factors that govern the supply and disposition of fatty acids, diacylglycerols, ceramides, cholesterol, phospholipids, and other intrahepatic lipids.
- **Energy oversupply and limited adipose tissue expansion** contribute to insulin resistance and metabolic disease
- **When energy intake exceeds metabolic need** (energy intake that comes in the body is more than the body consumes or uses), carbohydrate drive the formation and accumulation of intrahepatic fat.
- Other factors contributing to intrahepatic fat accumulation includes **type of fat consumed**, **genetic polymorphism**, **gut microbiome.** (genetic predisposition, type of food such as fructose are risk factors)
- Factors that controls **energy disposal** includes **frequency** and **intensity of exercise**, **caloric intake** and **activation** of **brown adipose tissue**.
- Other factors that can cause the disease is dietary food such as saturated fat food, **fructose**.

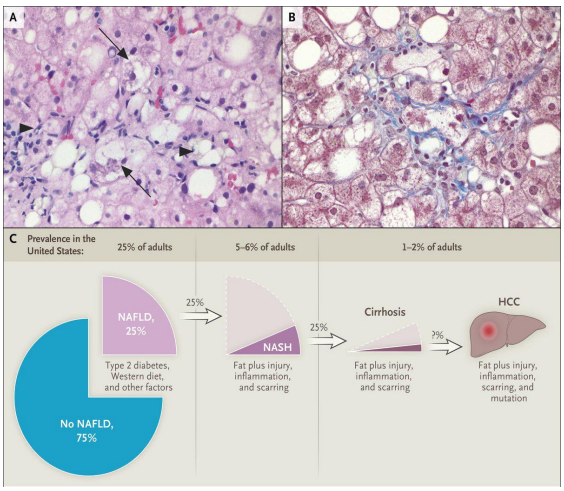
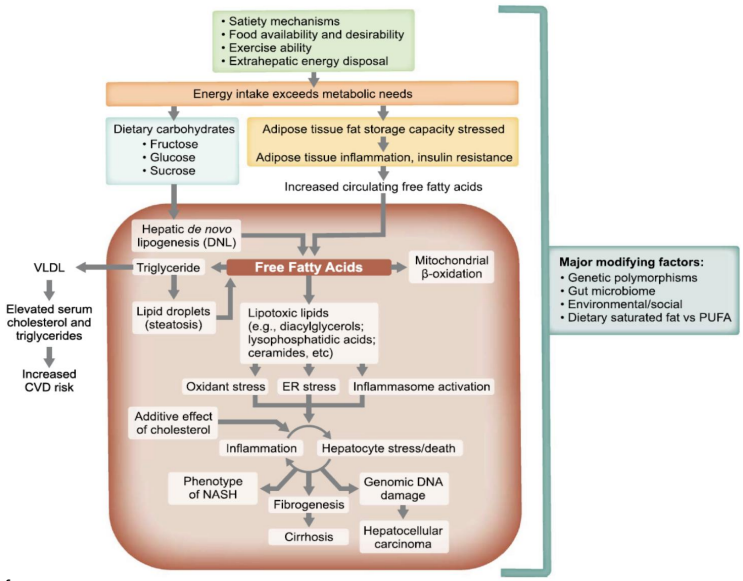


Figure 1. Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).
NASH is a potentially progressive type of nonalcoholic fatty liver disease (NAFLD). Panels A and B show characteristic histologic features of NASH in liver-biopsy specimens: ballooned hepatocytes (arrows), inflammatory infiltrate (arrowheads), and fibrosis. Panel C shows the relative distribution of NASH, cirrhosis, and primary liver cancer in the U.S. adult population. Data in Panel Care from Williams et al.' and Adams et al.' HCC denotes hepatocellula



Doctor said that you should know the **Natural History of the disease "progression". It is important to know it when you want to tell your patients about the prognosis.**
Just know that it is 25-25-25
About 25% have genetic predisposition in addition to the other risk factors can develop fatty liver. And 25% of them develop MASH and 25% of them develop cirrhosis.

(1): Pathogenesis:

- Patient has fats that goes to the liver -> FFA converted to TG -> TG carried on by VLDL -> VLDL goes to the tissue & get stored.
- So any of these steps inside the liver prevented (e.g. conversion of FFT or VLDL transport) will lead to accumulation of FFA
- FFA should not be accumulated in liver because FFA are **lipotoxgenic** which can cause inflammation

Fatty liver

◀ Diagnosis

Non invasive

History/ Physical

- **Rule out other comorbidities** (T2DM , HTN , DLP (dyslipidemia) , Obesity , ETOH (Alcohol), Drugs, Family HX)
- Vitals , BMI.

Labs

- AST/ALT with mild elevation (Very mild less than 100), if it is 500-600 then it is **not fatty liver** or it could be fatty liver but with other things
- Screen for comorbidities (T2DM , HTN , DLP , CVD)
- Exclude other causes of liver disease especially if you have elevated liver enzymes.

Slightly elevated liver enzymes indicate inflammation "MASH" but negative liver enzyme does not exclude inflammation

Biomarkers

An **objective patient characteristic** measured as an indicator of :

- Normal biologic process.
- Pathogenic process.
- Biological response to therapeutic intervention.

Table 1 Serum markers of liver fibrosis

Test	Components of panel	AUROC	Sensitivity (%)	Specificity (%)	Cutoff	NAFLD stage of fibrosis
AST/ALT ratio	AST, ALT	0.83	21	90	1	F3–F4
AST to platelet ratio index	AST, platelet count	0.67–0.94	30	93	0.45 (low cutoff) 1.5 (high cutoff)	F2–F4
BAAT score	BMI, age, ALT, serum triglycerides	0.84	71	80	2	F3–F4
BARD	Body mass index (BMI), AST/ALT ratio, and diabetes	0.8	86.8	32.5	2	F3–F4
ELF test	Age, HA, TIMP-1, PIIINP	0.82–0.90	80	90	8.5–11.35	F2–F4
FibroMeter	Platelet count, g2 macroglobulin, AST, age, prothrombin index, HA, blood urea nitrogen	0.90–0.94	81	84	F3: 0.61 (low cutoff) 0.71 (high cutoff)	F2–F4
FibroTest	Alpha-2 macroglobulin, haptoglobin, GGT, total bilirubin, apolipoprotein	0.81–0.92	15–77	77–90	0.3 (low cutoff) 0.7 (high cutoff)	F2–F4
FIB-4	Age, AST, platelet, ALT	0.88	26–74	71–98	1.3–1.92 (low cutoff) 3.25 (high cutoff)	F3–F4
Hepascore	Age, gender, bilirubin, gamma-glutamyl transferase (GGT), hyaluronic acid, and α2-macroglobulin	0.81 0.90	75.5 87	84.1 89	0.37 0.70	≥F3 F4
NAFLD fibrosis score	Age, hyperglycemia, BMI, platelet, albumin, AST/ALT ratio	0.81	51	96	F3–F4 −1.45 (low cutoff) 0.67 (high cutoff)	

INDIRECT SERUM MARKERS

- **FIB4: AST, ALT , PLT , AGE** (Most important one!)
  (<1.45 unlikely to have fibrosis)
  (>3.25 likely to have advanced fibrosis)

What is the uses of FIB4 (benefits)? Used in **screening tool in primary care** to decide if the patient needs for the referral to hepatologist.
If **FIB4** is **elevated (>2.67)** then the patient should be referred to hepatologist. If it is not elevated then there is no need for the referral.
If it is **less than 1.45** then it is managed in in primary care

- **APRI:** AST, PLT
- **NAFLD fibrosis score:** AGE, BMI , hyperglycemia, AST/ALT, PLT, Albumin
- **Others:** BAAT, BARD.

Which biomarker is more sensitive? FIB4

DIRECT SERUM MARKERS not used clinically because it is expensive. It is more common in research setting, don't focus on it

- **Fibrotest** (Age, gender, GGT, bilirubin, a2 macroglobulin, haptoglobin, apolipoprotein a1)
- **ELF test** (PIIINP, TIMP1, hyaluronic acid)
- **Fibrometer** (PLT, PT , AST, a2 macroglobulin, GGT , fibroscan)
- **Pro-C3**

Fatty liver

◀ Diagnosis

Non Invasive

IMAGING

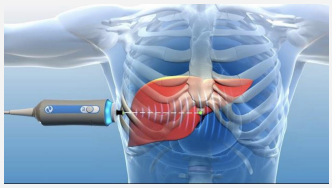
Fibroscan, US, MRI and Shear Wave elastography.

Quantifiable Parameters on Imaging: (What can we see on imaging?)

- Hepatic steatosis
- Fibrosis
- inflammation you can know that there is an inflammation but you **can not be 100% sure** that is NASH. Not accurate as biopsy.

1. **Vibration Controlled Transient Elastography (VCTE) It is fibroscan and it is not painful**

- Patented in 1999.
- It is most **commonly used.** It works like US, it sends sound waves that are reflected by the liver
- 2 Probs:
  - M (medium) probe : Skin-capsule distance <25 mm
  - XL (X large) probe : Skin-capsule distance 25-35mm
  (NO need to memorize the numbers. Medium and large sizes are used based on the weight of the patient)
- Controlled attenuation parameter (CAP) measures the increased attenuation of ultrasound waves when travelling through steatotic hepatic tissue, compared to normal liver (basically measures the liver fat)
- IQR: index of intrinsic variability parameter not IMP
- Ekpa : Measurement of liver stiffness.



Results interpretation: (You have to know how to interpret it)

CAP (written in blue) (indicates amount of **fat** on the liver):

> 300 = significant fatty liver

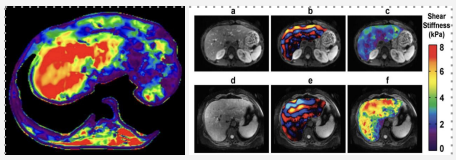
kPa (written in orange):

- The lower the number the better (Not good to have high KPa)
- Less than 5 is good and more than **15** is **advanced fibrosis**
- The numbers are not important (Just for you knowledge)

The goal of the fibroscan is to know if there high chances of advanced fibrosis or to exclude the fibrosis (more than to determine the degree of fibrosis)

2. **Magnetic Resonance Elastography**

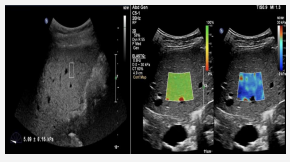
- It can measure MRI stargrophy
- It can measure the **fat burden** on the liver
- Detects **inflammation**
- Not commonly used



Magnetic Resonance Elastography
Increasing in **kPa** indicates that there is high degree of liver stiffness/fibrosis

3. **Shear Wave Elastography**

- Not commonly used



Fatty liver

◀ Diagnosis

Invasive

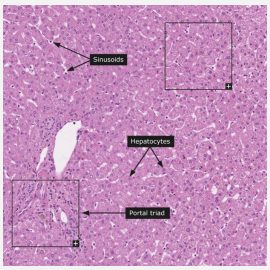
LIVER BIOPSY

1. **Biopsy:** (when to do biopsy?)
   - **Suspected other diagnosis** or **CLD** (Chronic Liver Disease) **cannot be excluded.**
   - NAFLD patients with higher risk of developing **steatohepatitis** or **advanced fibrosis**

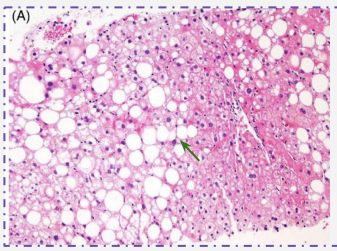
When do we do liver biopsy?

- e.g. if a patient has steatosis with high liver enzymes 200-300 and the other lab tests are negative and you don't have any other cause. In this case you can take a biopsy.
- Sometimes they use liver biopsy in control trails (research purposes) to know what is the best medication to use in a patient who has advanced liver fibrosis.

Normal liver biopsy

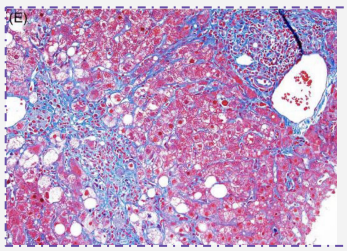


Abnormal liver biopsy



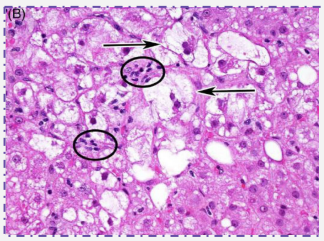
Macrovasicular Steatosis
"like goblet"

MASLD
Pure Steatosis



Fibrosis
(Blue color)

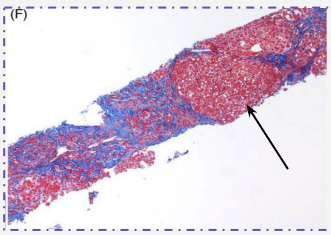
Reticulin stain is used to see the fibrosis. If we don't use this stain then we will NOT see the fibrosis.



Neutrophilic Infiltrate
(black circle)

Ballooning
(Black arrowhead)

MASH Parameters
(If you see neutrophilic infiltrate or ballooning you can think of **MASH**)



Nodules

Cirrhotic Liver
(Advanced, bridging fibrosis)

Treatment of Fatty liver

Lifestyle Modification

The most important treatment is lifestyle modification

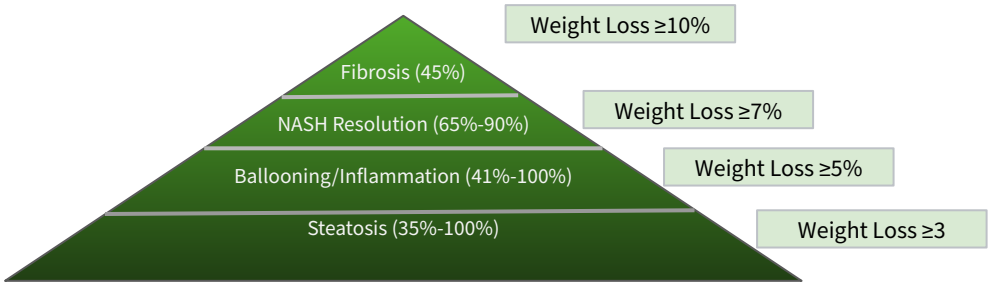
Exercise

- Regular or moderate exercise **at least 5 times per week for a total of 150 minutes per week** or an increase in activity level by more than 60 minutes prevent or improve NAFLD.
- Other studies Suggest more vigorous exercise routine needed to improve NASH histology.

Diet

- **Excess saturated fats, refined carbohydrates, sweetened beverages and fructose consumption** has been associated with NAFLD.
- Different Diets (low fat, intermittent fasting, Mediterranean diet) are comparable in improving NAFLD.
- **Mediterranean** diet is recommended due to the additional **Cardiovascular benefit**
  (The most important thing is calorie control)
- **>3 cups of coffee/ day may reduce the risk of NAFLD**. (Black coffee not latte :))

Weight loss and diet is the **Cornerstone** of NAFLD/NASH therapy 3-5%= steatosis improvement 5-7%= Inflammatory regression >10%= Fibrosis regression
More weight loss correlate with better outcome 3-5% improves the steatosis, 5-7% improves the inflammation, more than 7% improves the NASH, more than 10% is associated with fibrosis regression.



Medical/Surgical Weight Loss Intervention

Until today there is no FDA approval therapy for NASH! (When we talk about FDA approval that means that we are talking about the medication not the lifestyle modification because lifestyle modification doesn't need FDA approval)

Bariatric Intervention

- Acceptable in **BMI ≥ 40 or ≥35 with comorbidities** (Not for anyone, it has a **criteria**. The patient has to have high BMI with comorbidities)
- **Resolve NASH, without worsening of fibrosis** and it reduces all-cause mortality
- Restrictive bariatric surgery (ربط المعده) has a higher chance of NASH persistence than malabsorptive surgery (in which you reroute a portion of the small intestines to decrease the absorption).
- Endoscopic bariatric surgery is promising , but needs long term efficacy-safety data (New therapy)

Targeted Therapy

(There isn't very strong evidence on this therapy and not widely used)

Vit E

Pioglitazone

NASH first appeared in the 1980s and it was NOT the leading cause of cirrhosis. **Hepatitis C was the leading cause of cirrhosis** and liver transplant. (Also alcohol is a leading cause). In 2015 they have developed medications for HCV so the incidence of Hepatitis C reduced and no longer HCV is the leading cause of cirrhosis like before. So fatty liver took the upper hand in causing liver cirrhosis. Now NASH is the leading cause of liver cirrhosis in Saudi Arabia. In America, alcohol is the leading cause of cirrhosis, but by 2030 NASH is expected to be the leading cause of cirrhosis worldwide.
It is hard to do control trials (Research Studies) in developing a medication for NASH. The most promising drug that they are now working on it is **THR (Thyroxine analogue)**

Our Team

Team Leaders

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- *Maha Alzahrani*
- *Shatha Alshabani*
- *Mohammed Alzeer*
- *Refal Alamry*
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