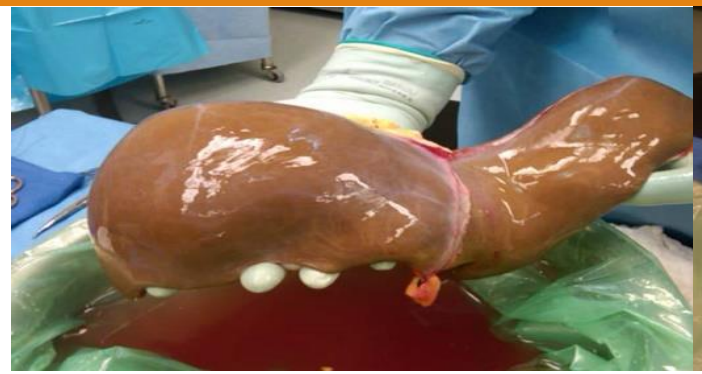
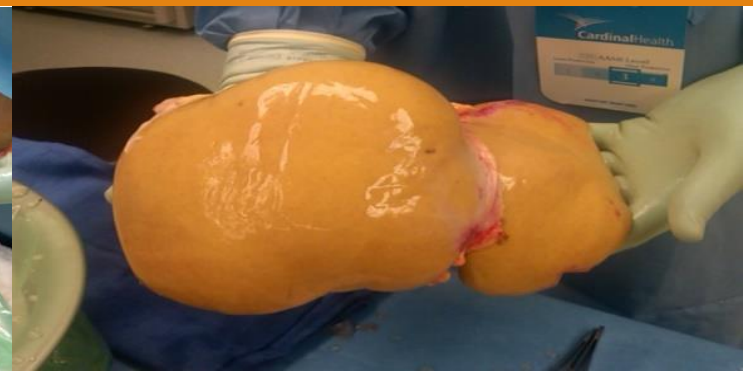
جامعة الملك سعود
King Saud University

Non-alcoholic Fatty Liver Disease (NAFLD)
MED 341





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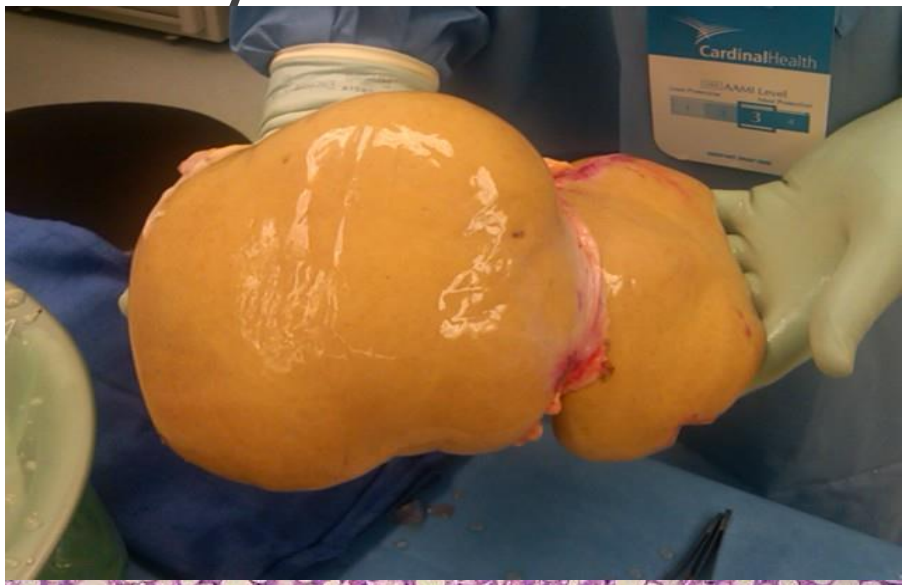
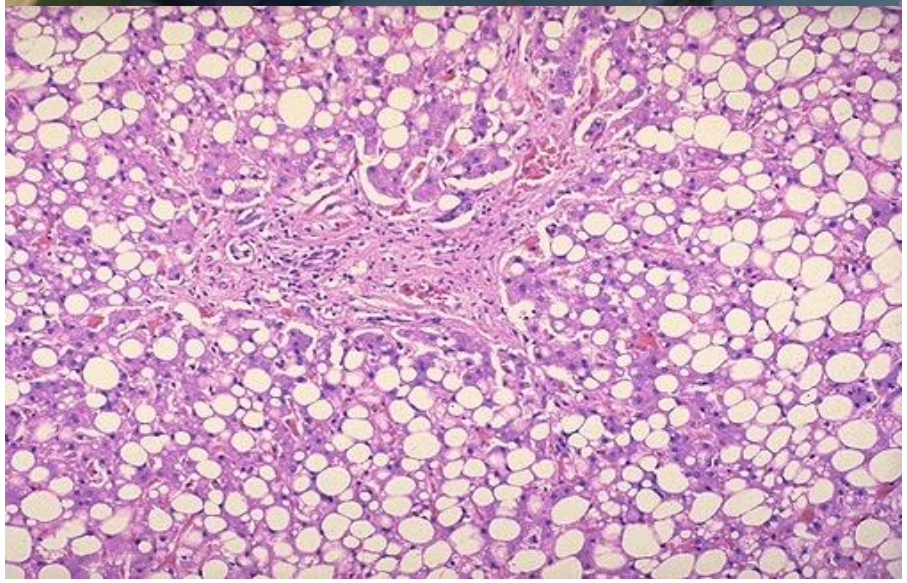
Objectives

To know and understand the following:

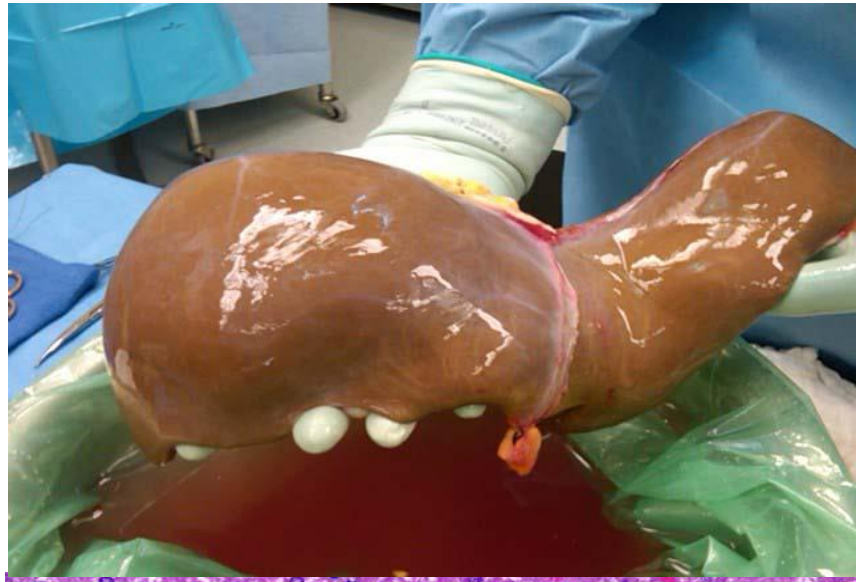
1. Definition, criteria for NAFLD, and disease spectrum
2. Epidemiology and risk factors
3. Pathophysiology of NAFLD, and natural history
4. Diagnosis and management approach

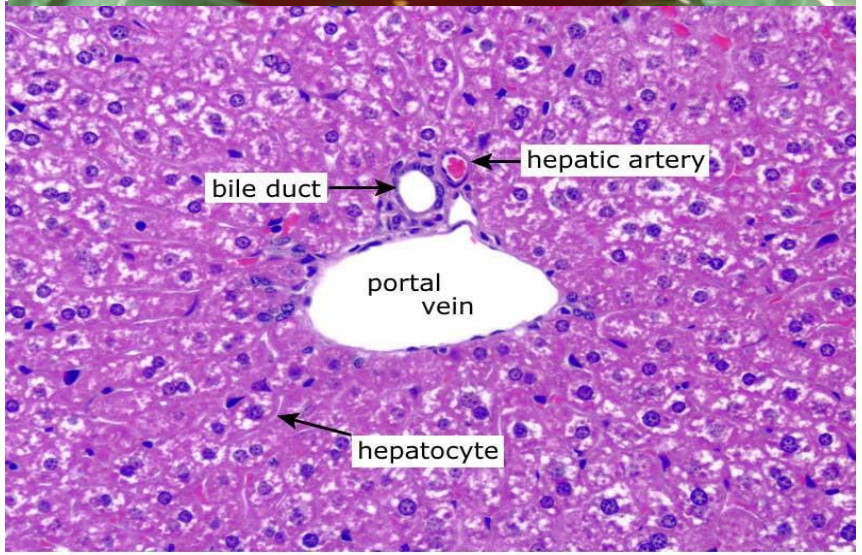
Fatty Liver





Normal Liver





NAFLD: Definition

Definition: Liver disease, where there is accumulation of excess fat in the liver cells, in people who drink little or no alcohol.

Criteria:

1. **Liver fat > 5%**
   - Estimated by cross-section on histology
   - Estimated non-invasively by MRI.

2. **Lack of secondary causes** of hepatic fat accumulation such as significant alcohol consumption*, long-term use of a steatogenic medications, or monogenic hereditary disorders, etc.

**Significant Alcohol use: daily alcohol consumption >30 g for men and >20 g for women.*

Classification of NAFLD (spectrum)

NAFL: Non-Alcoholic Fatty Liver

-Steatosis (no inflammation)

other terms: simple steatosis, benign steatosis

Non-progressive

NASH: Non-Alcoholic Steatohepatitis

-steatosis with inflammation, hepatocyte injury with or without fibrosis

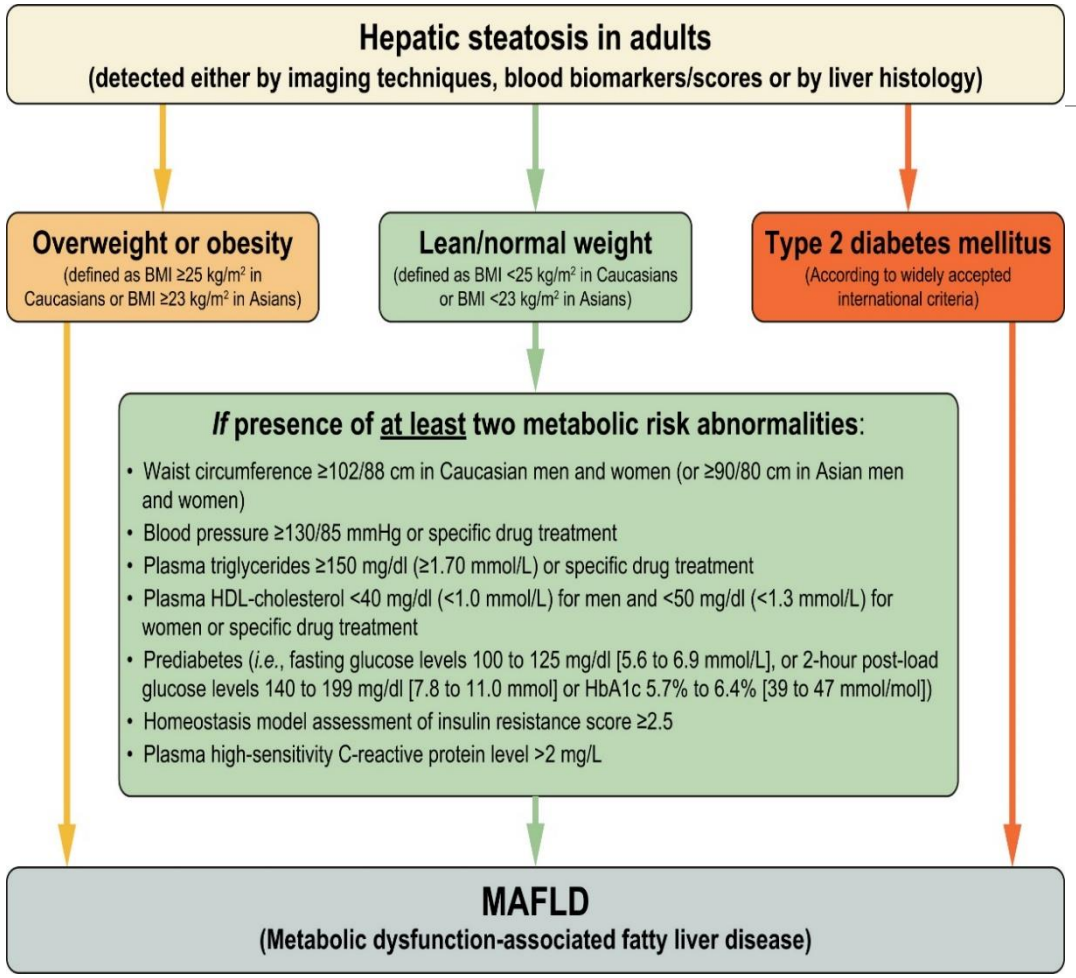
Progressive; cirrhosis , HCC

NAFLD Spectrum

Steatosis---------NASH--------NASH with fibrosis----------NASH cirrhosis (>>liver decomposition+-/cancer)

Sanyal, et al Hepatology 2011

Metabolic dysfunction-associated fatty liver disease or metabolic-associated fatty liver disease (MAFLD)



- This is a new proposed new definition gaining global acceptance
- MAFLD is defined as the **presence of hepatic steatosis** together with one or more of the following:
  1. Overweight or obesity
  2. Type 2 diabetes
  3. Two or more other metabolic risk abnormalities

Eslam M, et al. J Hepatol. 2020 Jul

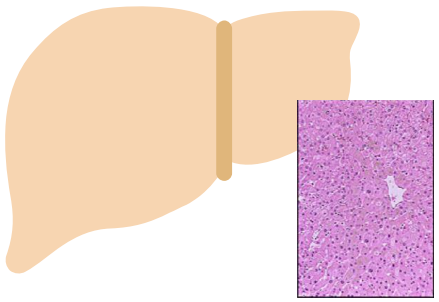
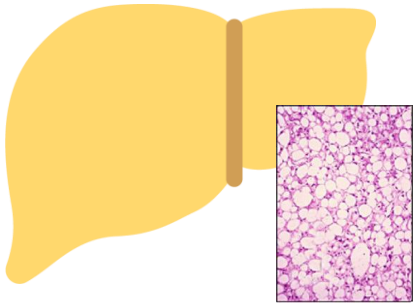
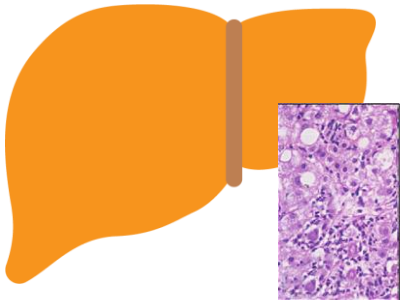
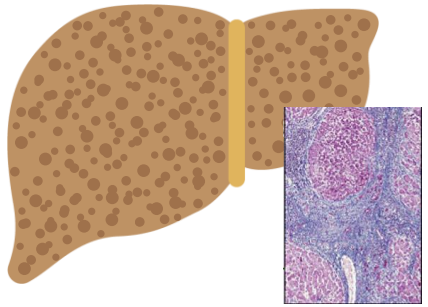
Fatty Liver Disease Burden

Global Burden of NAFLD

- More than one billion individuals worldwide have NAFLD
- Most common cause of abnormal liver tests
- Most common cause of chronic liver disease
- The second leading etiology of liver disease among adults awaiting liver transplantation in many countries (expected to be number one)
- Patients with NAFLD have increased overall mortality compared to matched control populations without NAFLD

Worldwide Prevalence of NAFLD and NASH

NAFLD

Normal Liver	Steatosis "NAFL"	Steatohepatitis "NASH"	Cirrhosis
			
	Fatty liver with trivial or no inflammation and no hepatocyte ballooning	Fatty liver with significant inflammation and hepatocyte ballooning	Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma
Worldwide prevalence:	25%[1]	3% to 5%[1]	1% to 2% at risk*

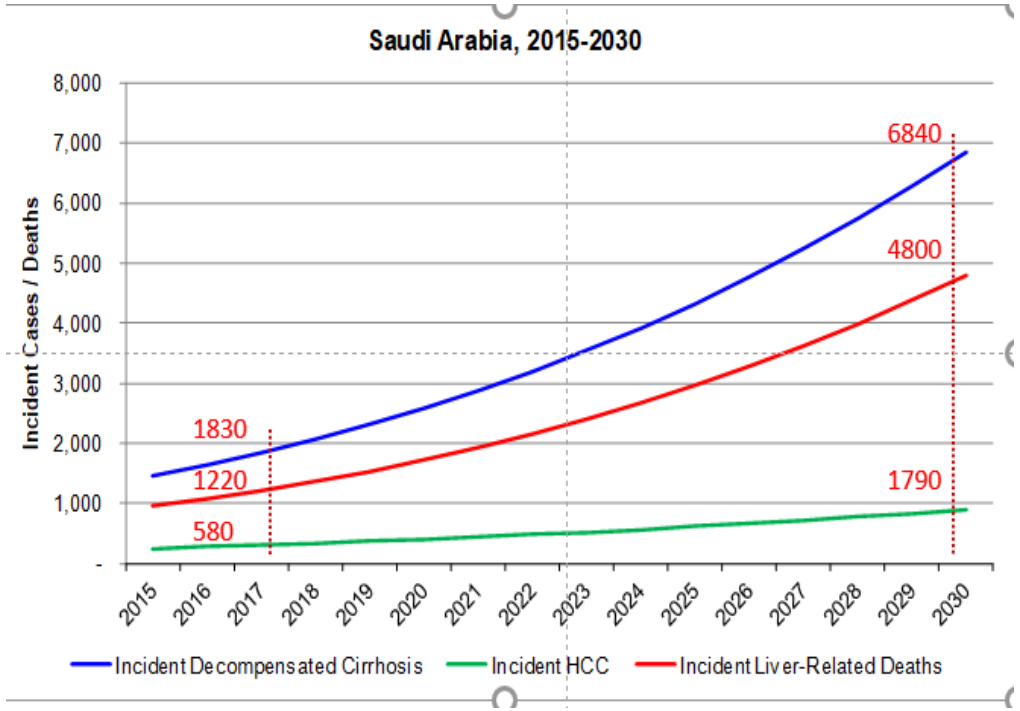
1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

Slide credit: clinicaloptions.com

NAFLD burden in Saudi Arabia

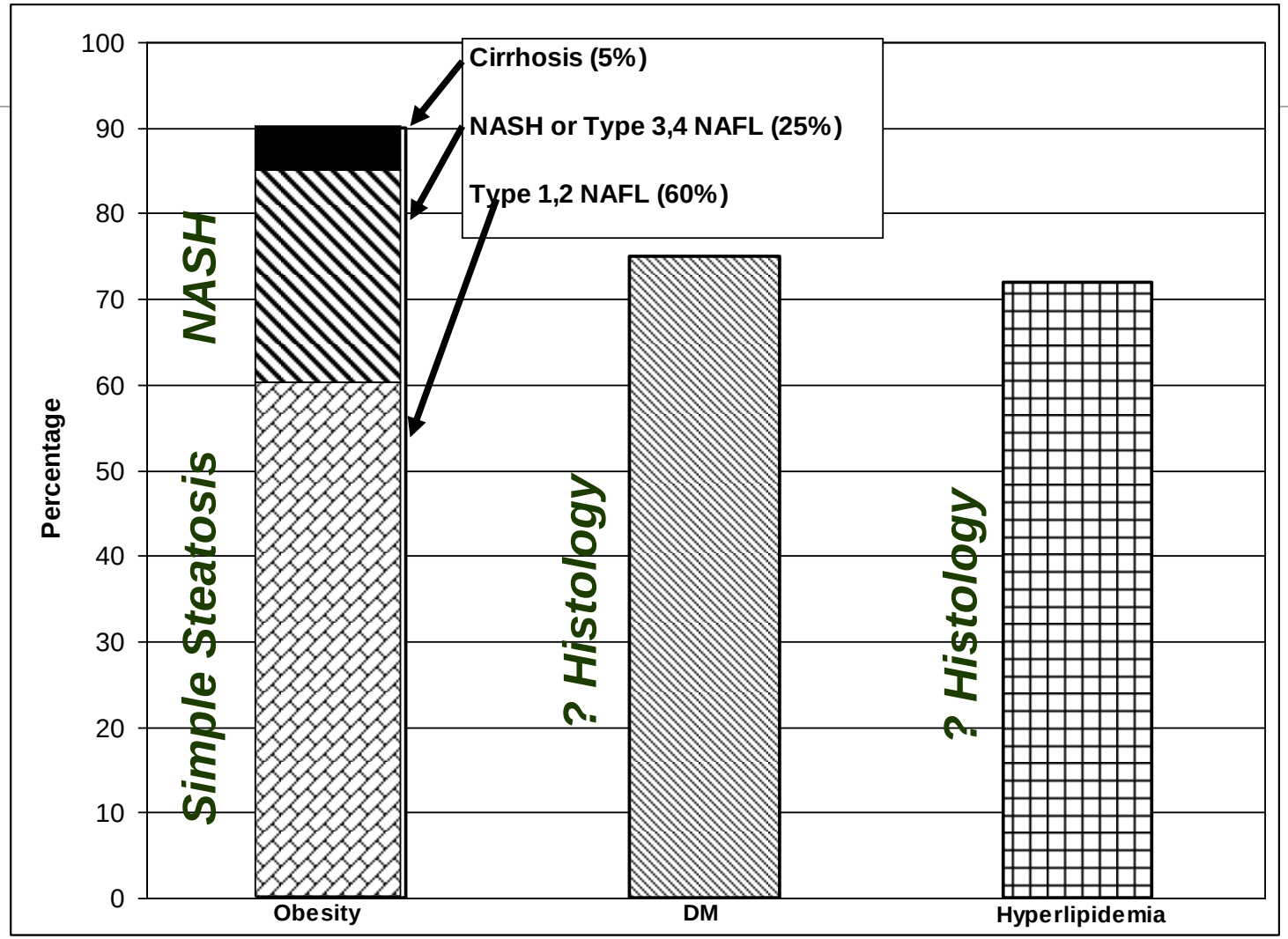
FUTURE DISEASE BURDEN 2017-2030

	2017	2030
Country Population (000)	32,900	39,500
NAFLD Total Cases	8,451,000	12,534,000
Prevalence (all ages)	25.7%	31.7%
NASH Total Cases	1,373,000	2,688,000
Prevalence (all ages)	4.2%	6.8%



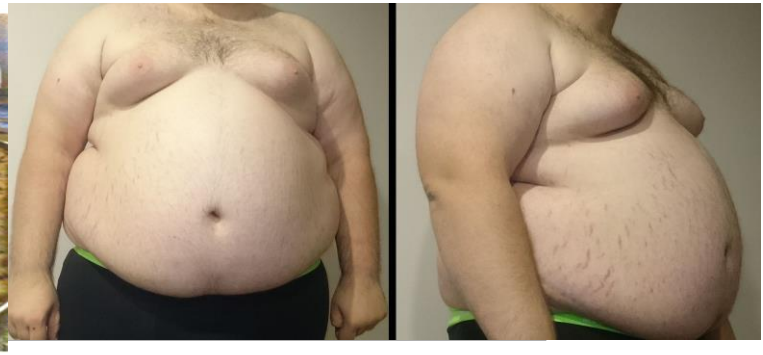
Alswat K, et al SJG, 2018

Prevalence is Higher in Risk Groups



Obesity *Diabetes* *Hyperlipidemia*

Risk factors



- Metabolic syndrome
- Insulin resistance
- Obesity (central)
- Type 2 Diabetes mellitus
- Hyperlipidaemia
- Male
- Medications (e.g Tamoxifen)
- Lifestyle (sedentary life style)

Comorbidity	NAFLD, %	NASH, %
Obesity	51.3	81.8
Type 2 diabetes mellitus	22.5	43.6
Dyslipidemia	69.2	72.1
Hypertriglyceridemia	40.7	83.3
Hypertension	39.3	68.0
Metabolic Syndrome	42.5	70.7

Younossi Z, et al Hepatology 2016

The American Diet

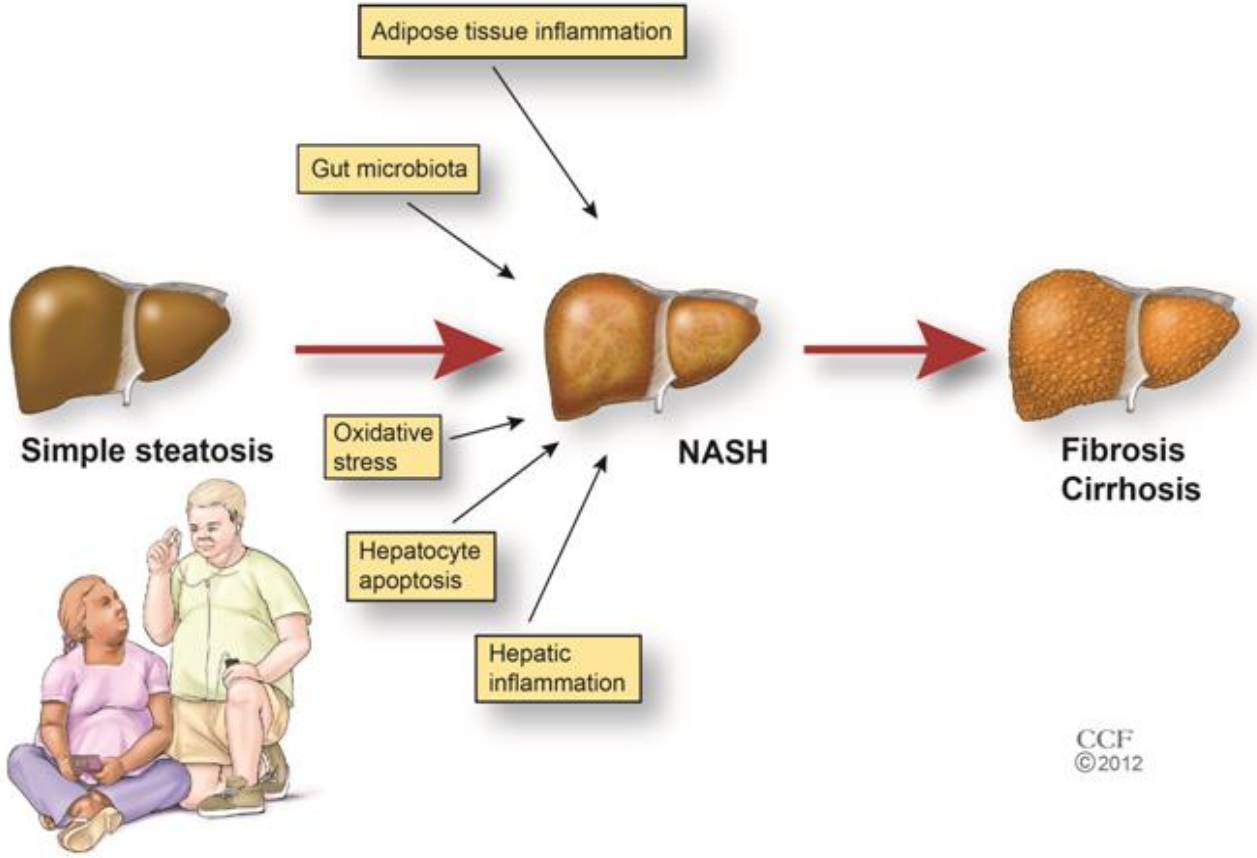
Significant Changes in the Past Half Century

Pathogenesis of NAFL AND NASH

Insulin resistance is the first step in most.

Insulin resistance leads to:

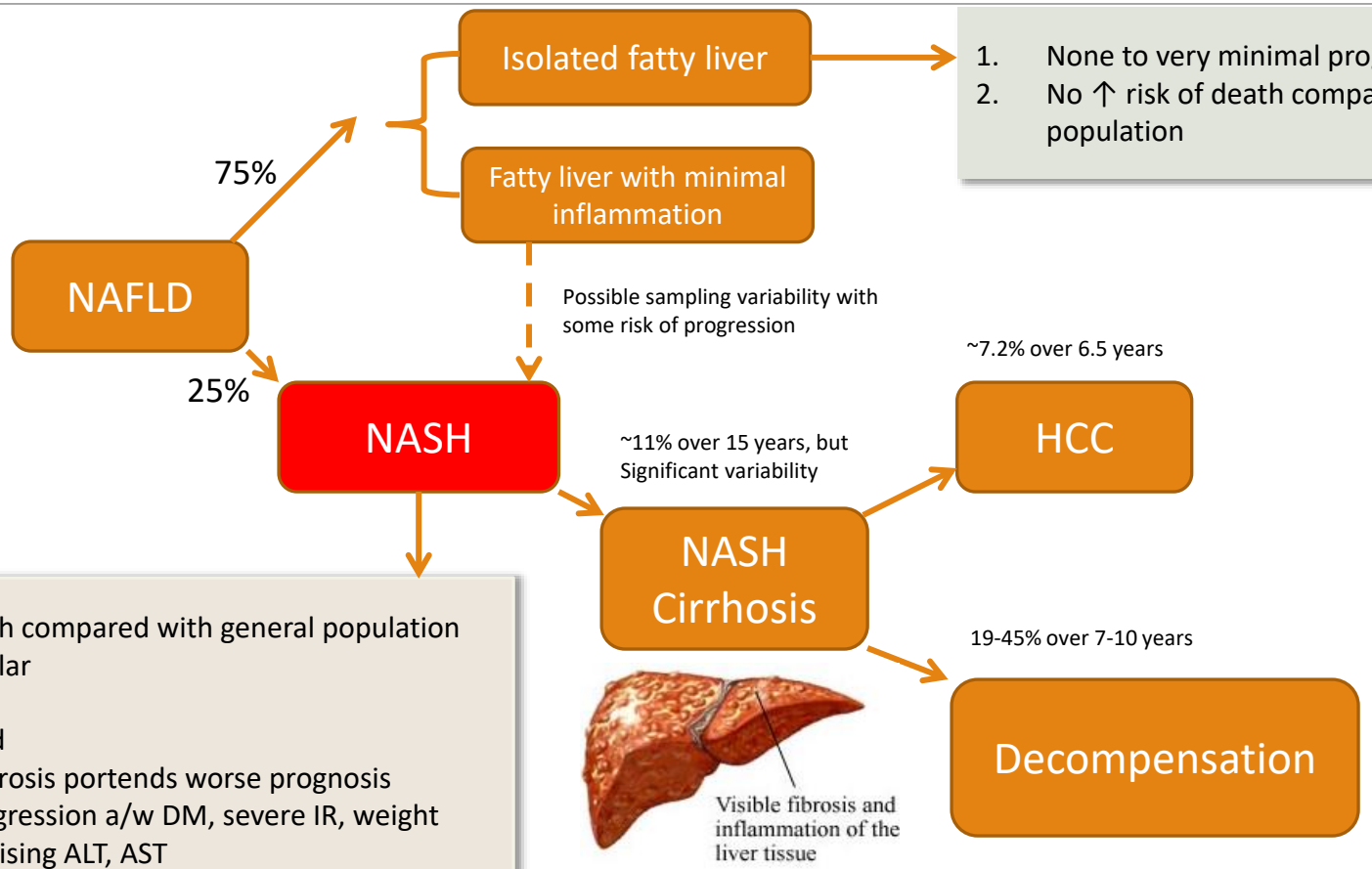
- Increased lipolysis>> FFA
- Increased hepatic uptake of free fatty acids (FFA) +
- De novo lipogenesis (e.g excess fructose >>accumulation of hepatic triglyceride.



https://gi.org/topics/fatty-liver-disease-nafld/

FFA: free fatty acids

Natural History of NAFLD



Modified from Torres DM et el. Features, diagnosis, and treatment of NAFLD. Clin Gastro Hepatol 2012;10:837-858.

Evaluation of patient with NAFLD

Evaluation of NAFLD Patient

HISTORY

- Symptoms

Most are asymptomatic (even with advanced disease)

  - Non-specific symptoms
  - Sometimes symptoms of liver decompensation are the first presentation

- Secondary causes:
  - Alcohol
  - Medications
  - other liver disease (viral , autoimmune etc.)

- Risk factors
  - Metabolic syndrome, DM, Hyperlipidaemia, hypertension, obesity etc.
  - Lifestyle (diet, activity)

EXAMINATION

- As any other liver disease
- BMI, OBESITY, Signs of decompensation etc..

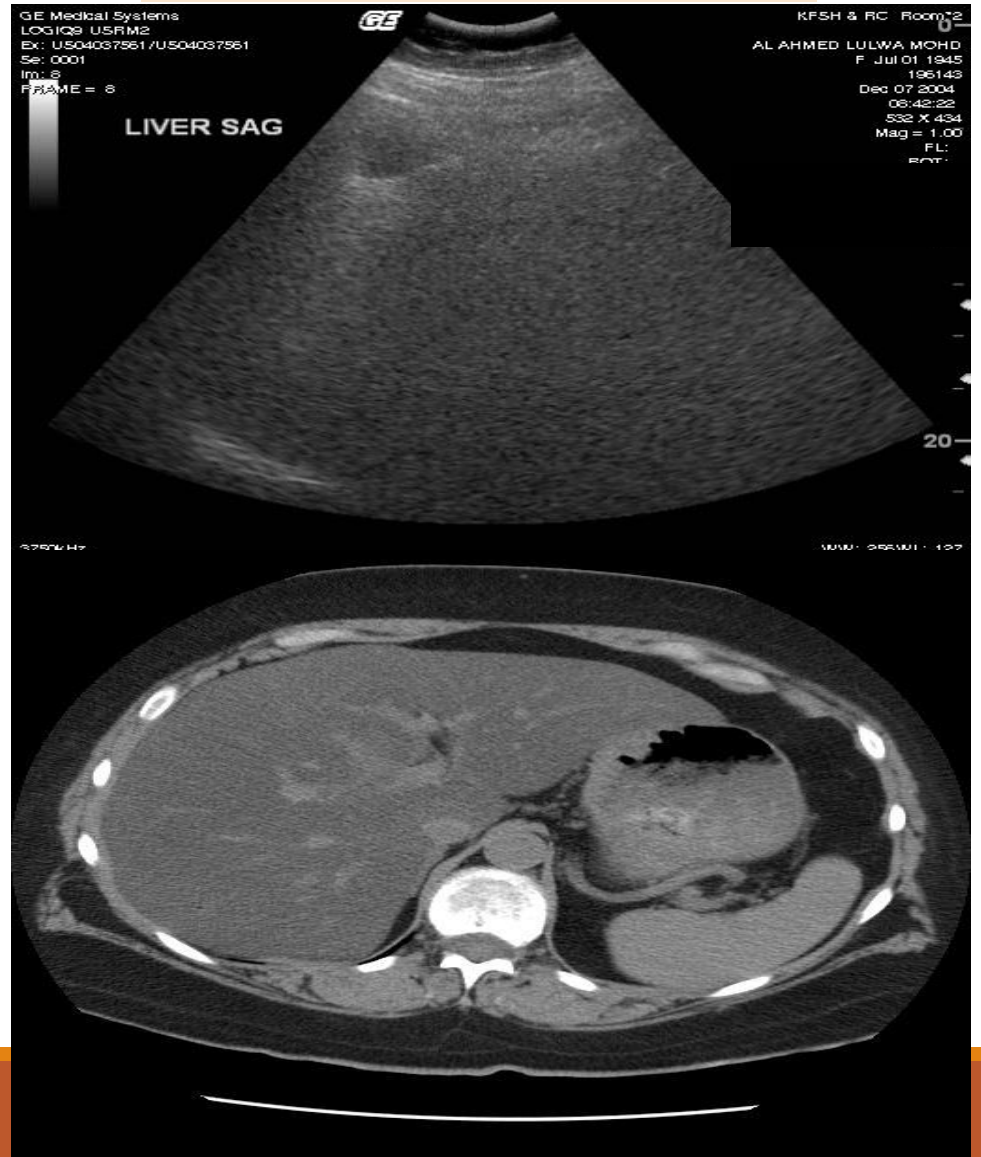
INVISTIGATIONS

- CBC
- LFT; mild rise in enzymes, can be normal
- INR, albumin, bilirubin
- Exclude other causes: HBV, HCV, autoimmune , Wilson etc

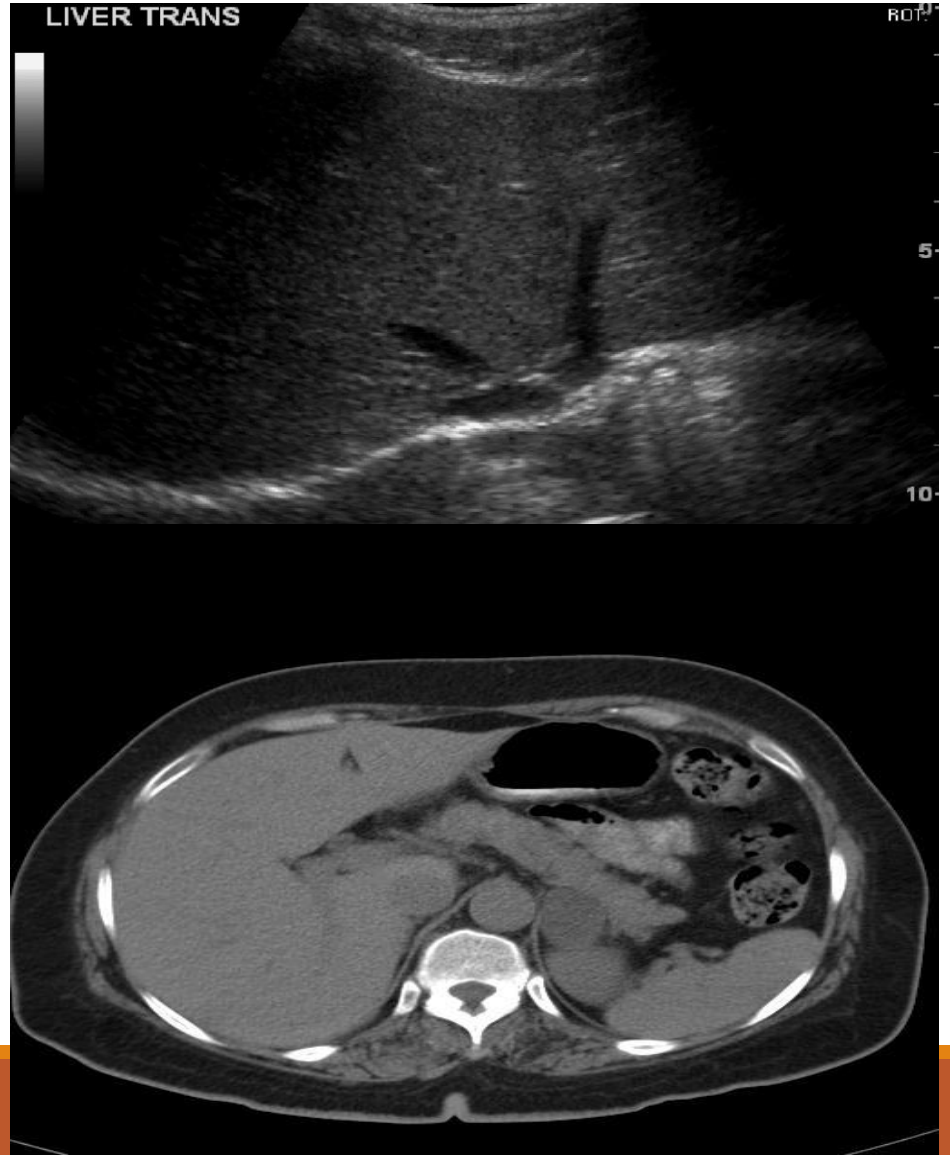
- US
- Fibrosis assessment (usually non-invasive methos
- Liver biopsy in some

Fatty Liver:

- bright liver on US,
- hypodense on CT



NORMAL



Fibrosis assessment

Degree of fibrosis is the most important factor in prognosis

Assessment

1. Non-invasive methods
   - Liver elasticity (e.g fibroscan)
   - Non-invasive serum markers scores
2. Liver biopsy (gold standard for NASH)

Example of noninvasive scores NB (for your knowledge only)

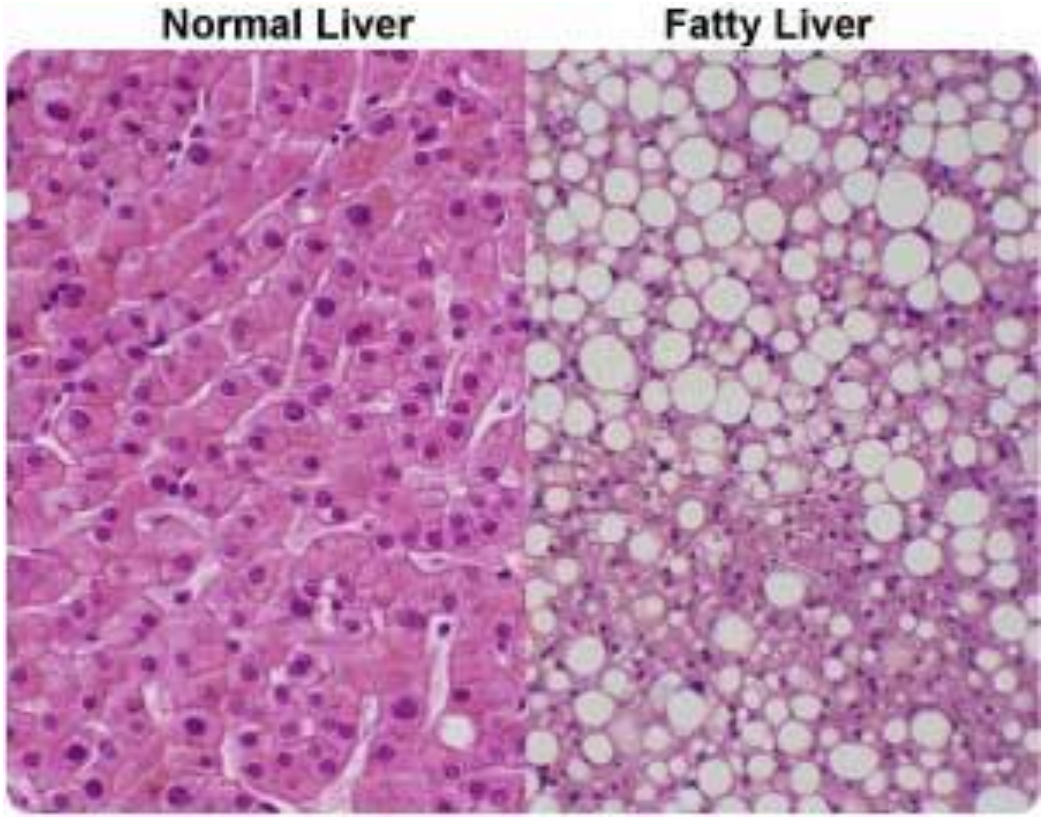
Test	components	equation
Fibrosis-4 (FIB-4)	Platelet count, AST, ALT, age	https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis.
APRI **A**ST to **P**latelet **R**atio **I**ndex (APRI)	AST, Platelet count	https://www.hepatitisc.uw.edu/page/clinical-calculators/apri.
NAFLD Fibrosis Score (NFS)	Age, BMI, platelets, albumin, AST/ALT, IFG /diabetes	https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score

Role of Biopsy

GOLD STANDARDS FOR DIAGNOSIS OF NASH- but not needed routinely

When?

- Confirm diagnosis
- Determine disease activity and fibrosis stage
- Exclude other diagnosis (when there is possibility of existence of other liver disease)



NAFLD Management

Targets

1. Liver disease
   - Reduce fibrosis, inflammation (NASH), and steatosis

2. Mange other associated metabolic disorders
   - Obesity
   - insulin resistance and DM
   - hyperlipidemia

Therapeutic modalities :

- Life style modification and weight loss

  (Cornerstone Management)

- Pharmacological
  - No FDA approved Therapy

- Surgical

Lifestyle modifications (most important step)

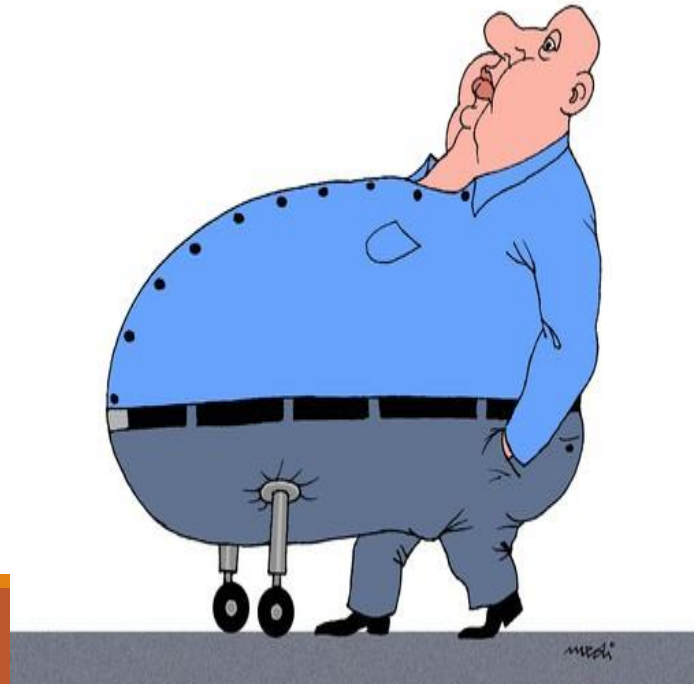
Lifestyle modifications

Lifestyle changes:

- weight loss
- exercise
- dietary modification

should be recommended as the primary intervention for NAFLD

- Weight loss, diet and exercise are the only intervention with established strong evidence suggesting it is benefit and safety, with a clear dose-response association regardless the type of exercise
- lifestyle changes(reduce associated risk factors)
- **Other measures; stop alcohol (for who drinks)**
- **Treat other conditions (DM, Hyperlipidemia.. Etc)**



✓ **Consistently beneficial *if sustained***
- ≥ 5% weight loss **Steatosis**
- ≥ 7% weight loss **NASH**
- ≥ 10% weight loss **Fibrosis**

✓ **Beneficial without weight loss**
- Reduce liver fat
- NASH and fibrosis (some evidence)
- Reduce risk for HCC

-Low glycemic food with increased mono and polyunsaturated

-Avoid high fructose containing foods

✓ **Aerobic & Resistance activity independently**:
- Reduce liver fat
- NASH and fibrosis (little evidence)

Hickman IJ, et al. Gut. 2004;53(3):413.
Katsagoni CN, et al Metabolism. 2017 Mar;68:119-132.
Promrat K, Hepatology. 2010 Jan;51(1):121-9.

Other methods of weight reduction

Not all are successful in lifestyle changes

Other ways of weight reduction

>>**BARATRIC SURGERY**

- Resolution of steatosis
- Resolution of NASH
- Resolution of fibrosis (in some)
- Improve other comorbidities, e.g DM

Pharmacologic Therapy of NAFLD

Pharmacotherapy

- ✓To improve insulin sensitivity
- ✓Reduce oxidative stress effect
- ✓Stop/slow necro-inflammation/fibrosis
- ✓Improve underling metabolic syndrome

NO FDA approved drug

Timing of Drug Action*

Obeticholic Acid
FXR Agonist

Elafibranor
PPAR a/d

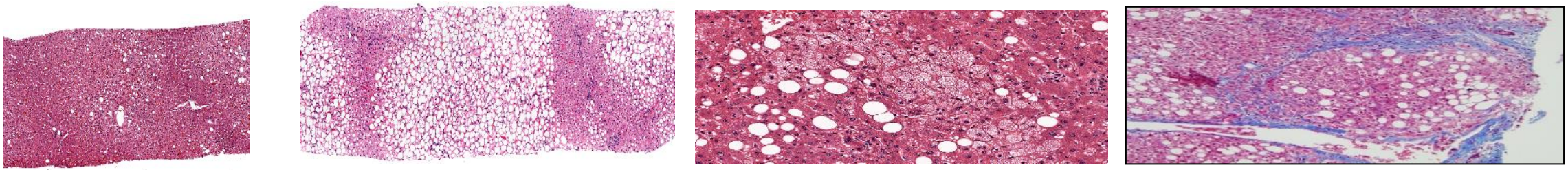
Vitamin E
Antioxidant

Liraglutide
GLP-1

Pioglitazone
PPAR y

Selonsertib
ASK-1 Inhibitor

Cenicivirоc
CCR2/CCR2



Normal Liver → Steatosis → Inflammation/Apoptosis → Fibrosis

**Medications either in phase 3 clinical trials, OTC, or not FDA approved for NASH indication*

Summary of management
Lifestyle modification to all + -

Intervention	Indication	Concerns
Bariatric surgery	Obese individuals with NAFLD or NASH.	
Vita E	Biopsy-proven NASH, Non-diabetic (Discuss benefits and risks)	Mortality Hemorrhage Prostate ca
Pioglitazone	Biopsy-proven NASH with or w/o DM (Discuss benefits and risks)	Wt gain, osteoporosis Balder cancer
Obeticholic acid	Still further data needed	Increase cholesterol Rebound weight gain
Liraglutide	No enough data to recommend	
Metfromin **Ursodeoxycholic acid** **Omega FA**	Not recommended	

Care Pathway And Risk Stratification

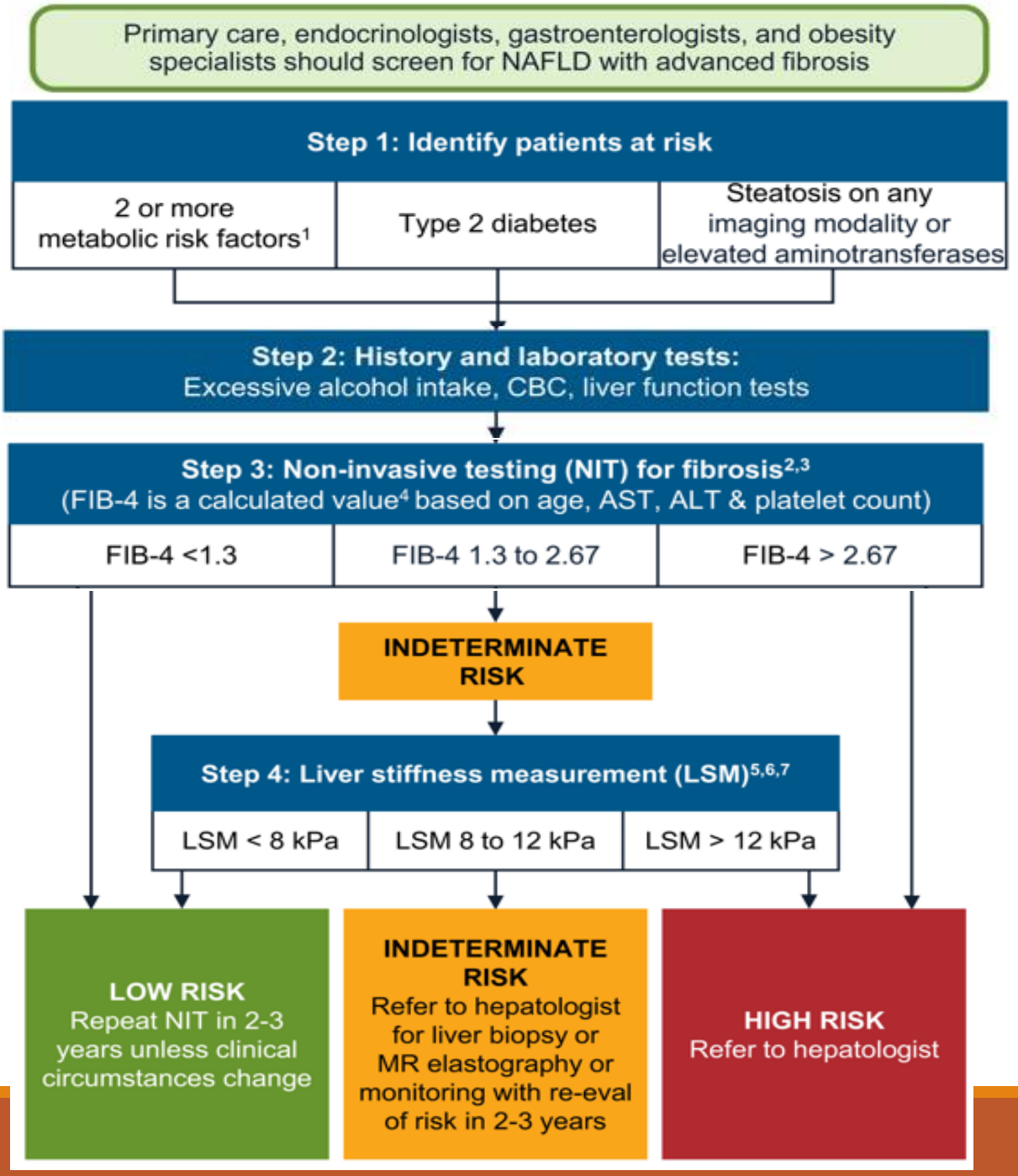
Screening for advanced fibrosis related to NAFLD/NASH.

Hepatic fibrosis is the most important determinant of liver and non-liver outcomes in patients with NAFLD

3 groups known to be at greatest risk of NAFLD/NASH-related fibrosis.

1. Patients with T2D
2. Patients with 2 or more metabolic risk factors
3. Patients with incidental finding of hepatic steatosis or elevated aminotransferases

- Nearly 10% of patients screened based on Steps 1 to 4 will have a high risk of clinically significant liver fibrosis



Kanwal F, et al. Gastroenterology. 2021 Nov

Summary

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Thank You.....