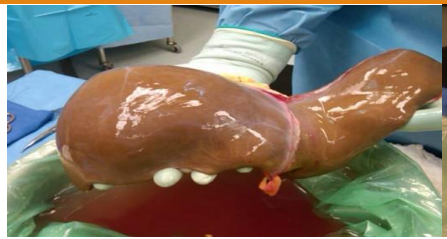
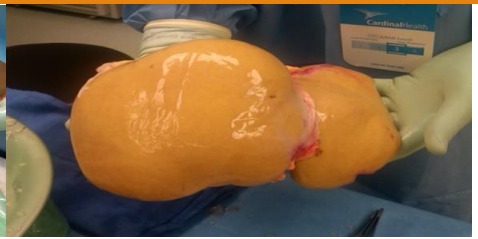
جامعة الملك سعود
King Saud University

Non-alcoholic Fatty Liver Disease
MED 341





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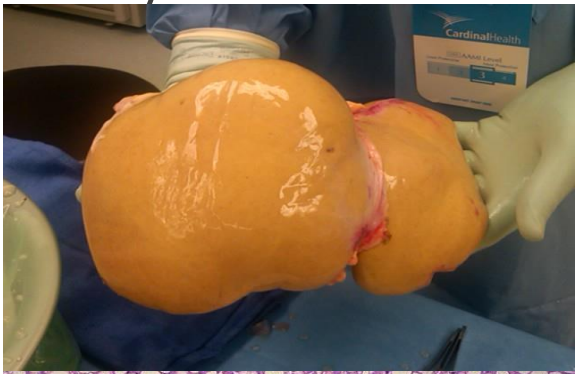
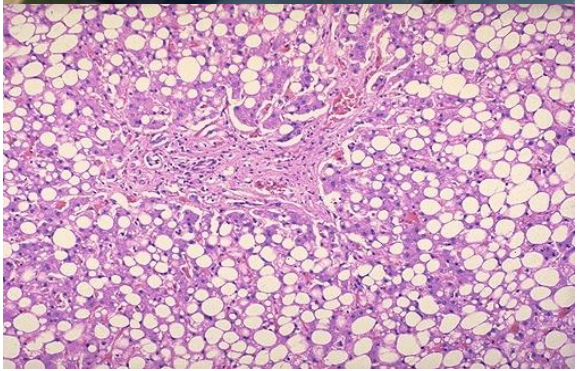
Objectives

To know and understand the following:

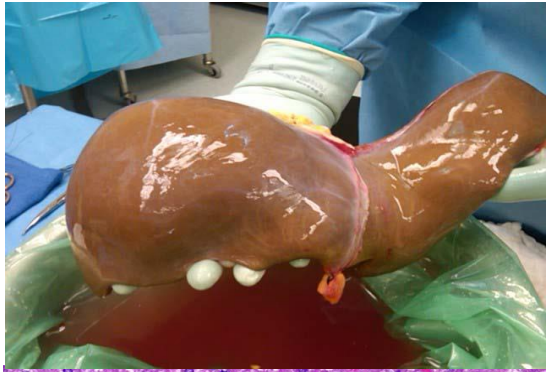
1. Definition, criteria for NAFLD, and disease spectrum
2. Epidemiology and risk factors
3. Pathophysiology of NAFLD, and natural history
4. Diagnosis and management approach

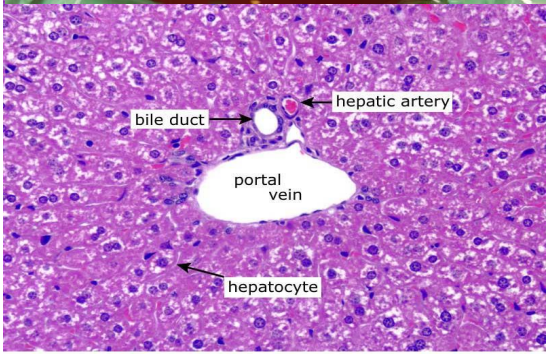
Fatty Liver





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

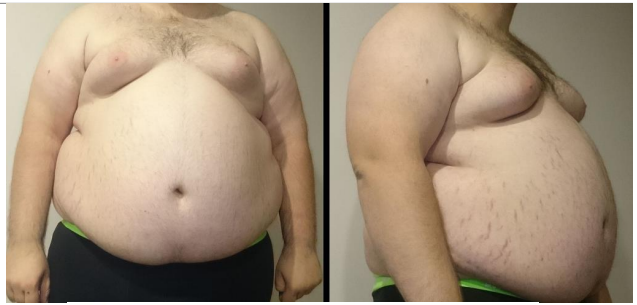
NAFLD Spectrum

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

Sanyal, et al Hepatology 2011

Risk factors

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



The American Diet

Significant Changes in the Past Half Century

Global Burden of NAFLD

- 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

Global epidemiology of NAFLD

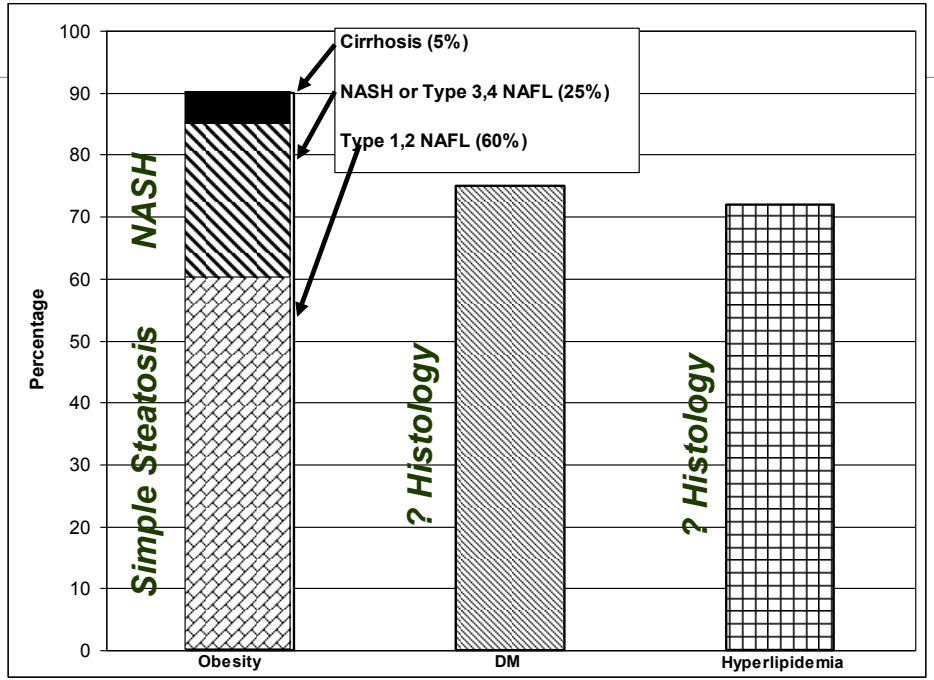
Global prevalence of NAFLD prevalence was 21.3% (17.9%-30.5%); **=20%**

NASH was prevalent in 26.2% of NAFLD patients

Asia	**24%(19.6%-30.5%);**
Europe	**21%(12.7%-31.7%);**
Middle East	**31.8% (13.5%-58.2%);**
North America	**18.5% (14.3%-23.6%);**
South America	**35.3% (27.8%-43.5%)**

Koeing et al . Hepatology 2015; 62 supl) 1286 A

Prevalence is Higher in Risk Groups



Obesity *Diabetes* *Hyperlipidemia*

NAFLD expected cases

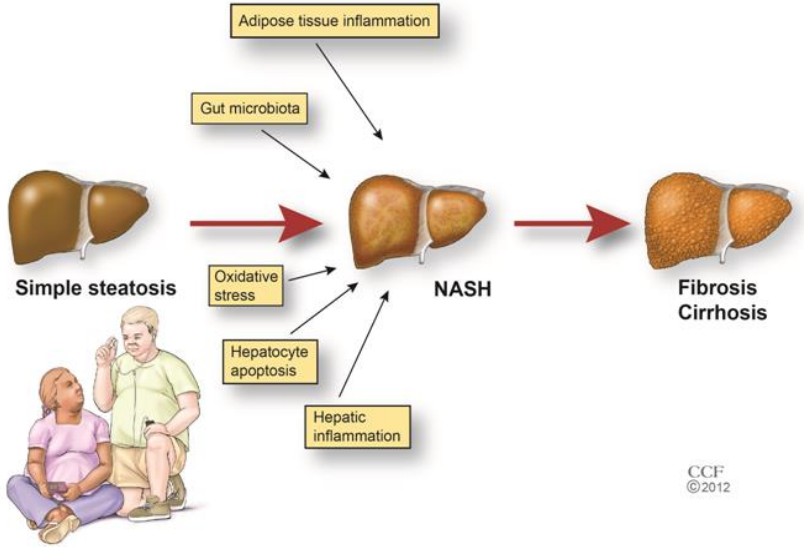
	2017	2030
Country Population (000)	32,900	39,500
NAFLD Total Cases	8,451,000	12,534,000
Prevalence (all ages)	25.7%	31.7%
NAFL Total Cases	7,078,000	9,846,000
Prevalence (all ages)	21.5%	24.9%
NASH Total Cases	1,373,000	2,688,000
Prevalence (all ages)	4.2%	6.8%

Pathogenesis of NAFL AND NASH

Insulin resistance is the first step in most.

Insulin resistance leads to:

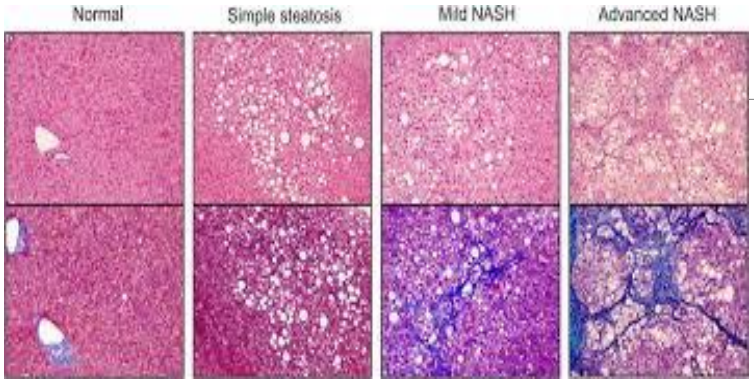
- Increased lipolysis>> FFA
- Increased hepatic uptake of free fatty acids (FFA) +
- De novo lipogenesis (e.g excess fructose >>accumulation of hepatic triglyceride.

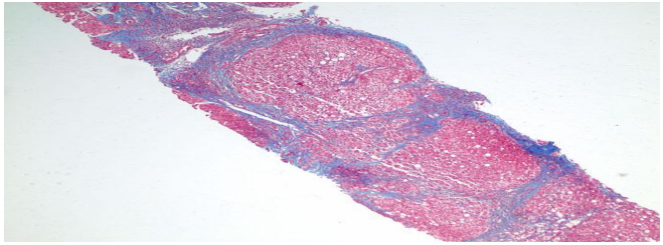


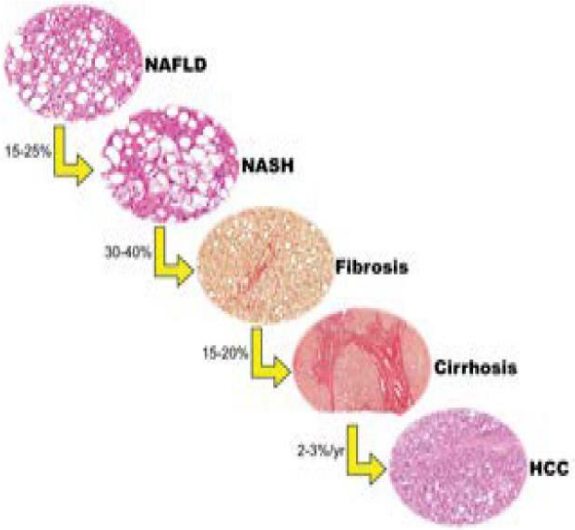
https://gi.org/topics/fatty-liver-disease-nafld/

FFA: free fatty acids

NAFLD spectrum and progression

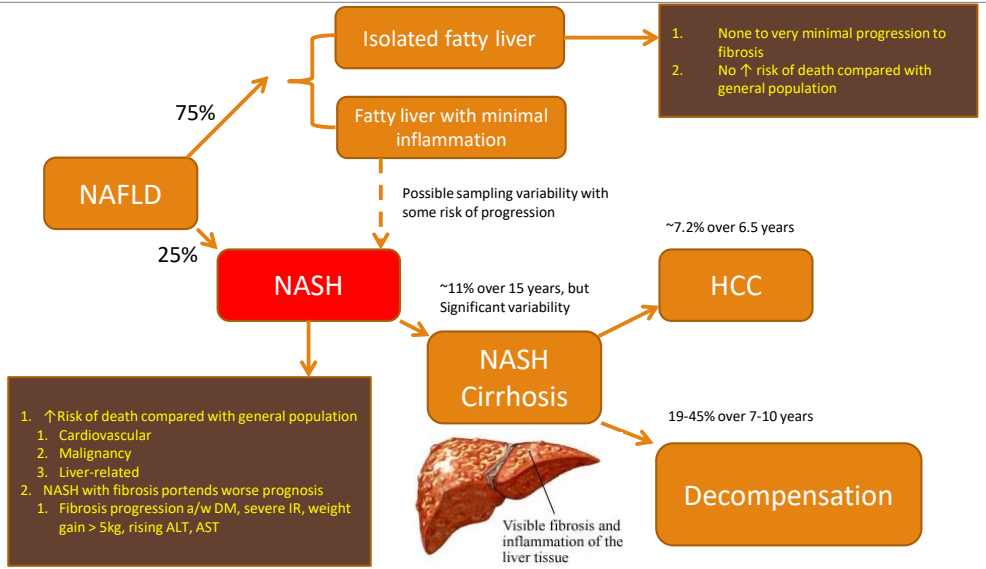






Nagaya T, et al J Hepatol. 2010 Oct;53(4):724-31.
Wang L, et al Disease. Int J Dig Dis. 2016, 2:1.

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

Assessment

Symptoms

Most are asymptomatic (even with advanced disease)

- Non-specific symptoms
- Sometimes symptoms related to associated conditions (DM, Obesity etc..)
- Sometimes symptoms of liver decompensation are the first presentation

Physical exam

- Abdominal obesity
- Enlarged liver
- Signs of cirrhosis/decompensation

Labs

- Consistent with metabolic syndrome
- Normal LFT
- OR Elevated bilirubin, AST, ALT, AP, GGT

Imaging

- Ultrasound Abdomen:
  - Enlarged liver
  - Increase echogenicity (bright)

Evaluation of NAFLD Patient

HISTORY

Symptoms

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

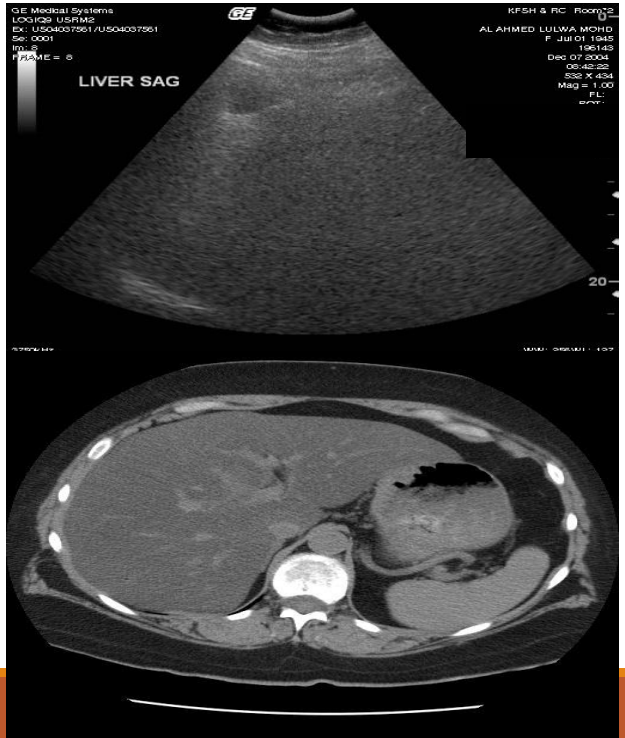
INVISTIGATIONS

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

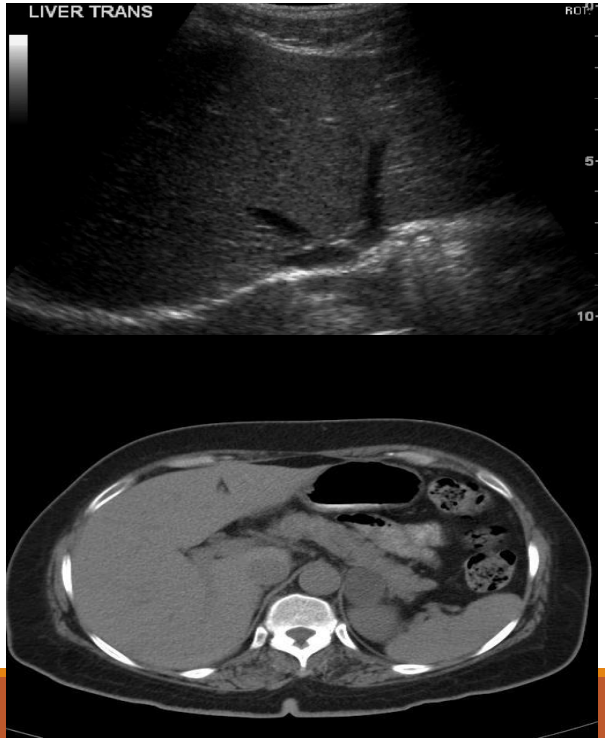
US
Fibrosis assessment (usually non-invasive methos

Liver biopsy in some

Fatty Liver



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

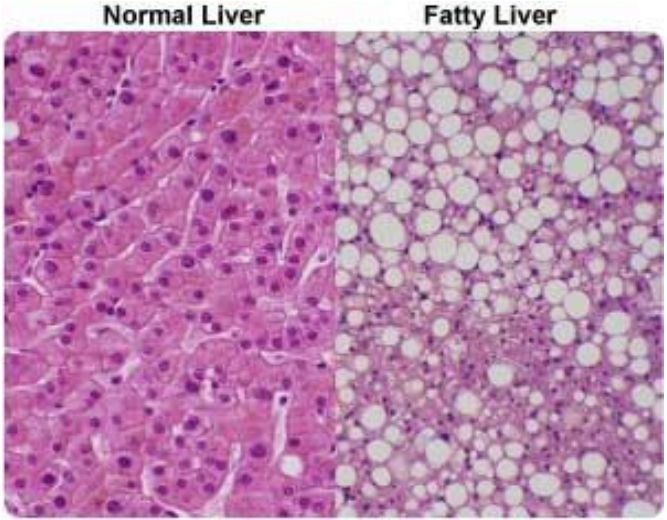
GOLD STANDARDS FOR DIAGNOSIS OF NASH- but not needed routinely

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)

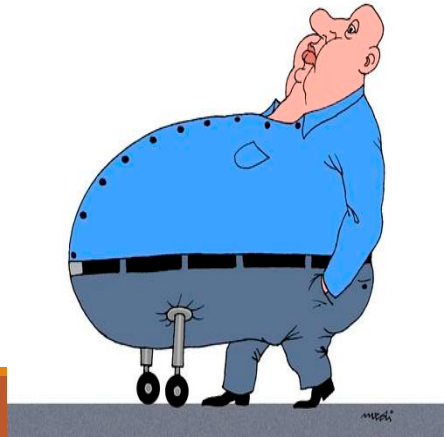
Lifestyle modifications

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

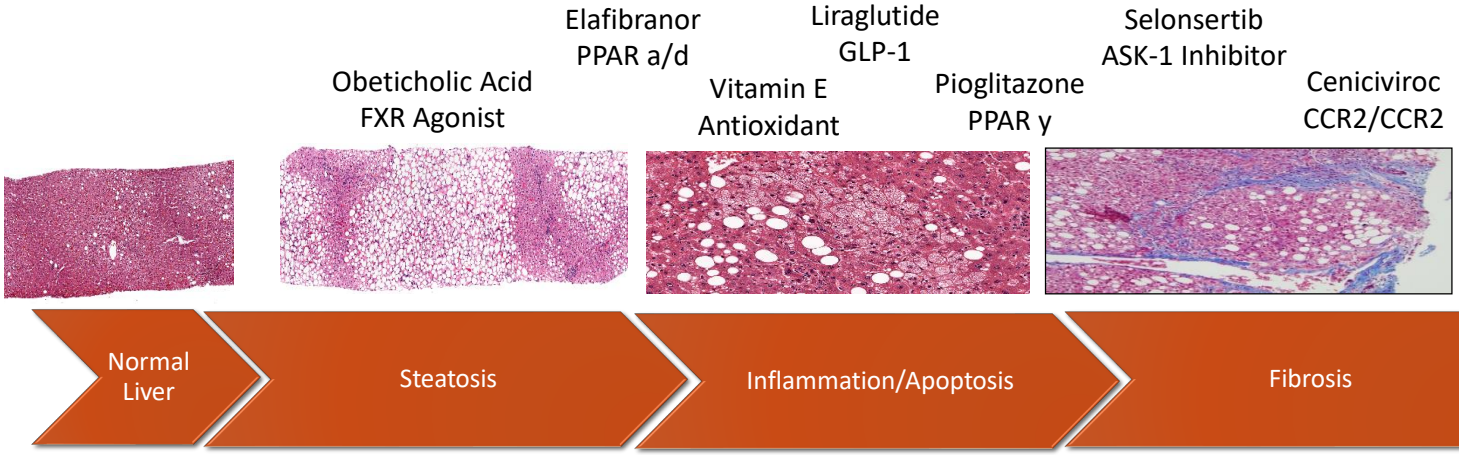
Pharmacologic Therapy of NAFLD

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*



**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	

Thank You.....