Lecture 27

Editing file

Medicine Team

Reviewed By

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Non-Alcoholic Fatty Liver Disease (NAFLD)

Objectives:

- ★ Definition, criteria for NAFLD, and disease spectrum.
- ★ Epidemiology and risk factors
- ★ Pathophysiology of NAFLD, and natural history
- ★ Diagnosis and management approach
- ★ Clinical approach to NAFLD patients

Color index:

Original text Females slides Males slides
Doctor's notes Text book Important Golden notes Extra

Introduction to NAFLD

Introduction

- Non-alcoholic fatty liver disease (NAFLD) is common medical condition globally and increasing in incidence with the epidemic of **obesity** and, **metabolic syndrome**[1].
- The leading cause of liver cirrhosis and liver transplantation in many countries.
- **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
- Non-invasively by MRI.

2

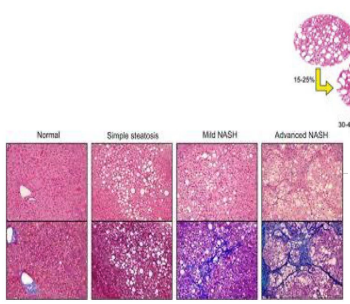
Lack of secondary causes of hepatic fat accumulation, such as:
- Significant **alcohol consumption** (daily alcohol consumption **>30g** for **men** and **>20 g** for **women**).
- Long-term use of a **steatogenic medications**.
- Monogenic **hereditary disorders**.

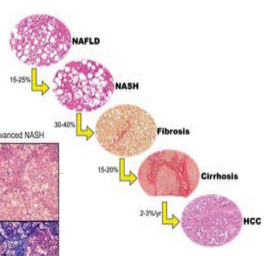
Classification of NAFLD

NAFL Non-Alcoholic Fatty Liver	NASH Non-Alcoholic Steatohepatitis
• **Steatosis** (**no inflammation**) other terms: simple steatosis, benign steatosis • **Non-progressive**	• **Steatosis** with **inflammation**[2], hepatocyte injury with or without fibrosis • **Progressive**: Cirrhosis, HCC

◀ Disease spectrum

NAFL (Steatosis) → **NASH** → **NASH with fibrosis** → **NASH cirrhosis (liver decomposition +- /cancer)**





1- NAFLD is also associated with polycystic ovary syndrome, obstructive sleep apnoea and small-bowel bacterial overgrowth.
2- Characterized by necroinflammation (**Hepatocyte ballooning, Mallory-Denk bodies, megamitochondria**). Cellular damage triggers cell death and inflammation, which leads to stellate cell activation and development of hepatic fibrosis that culminates in cirrhosis. **Perisinusoidal fibrosis** is a characteristic feature of NASH. Several genetic modifiers of disease severity have been identified, with PNPLA3 and its product, adiponutrin, being the best validated.

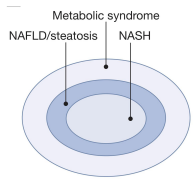
Risk factors & Global burden of NAFLD

◀ Risk Factors

- NAFLD is considered by many to be the hepatic manifestation of the **'metabolic syndrome'**, as it is strongly associated with:

1 **Insulin resistance**	**4** **Hyperlipidaemia**	**7** Lifestyle (sedentary lifestyle)
2 **Obesity (central)**	**5** Male	**8** Western diet
3 **Type 2 Diabetes mellitus**	**6** Medications (e.g Tamoxifen)	**9** Hypertension

◀ Global burden

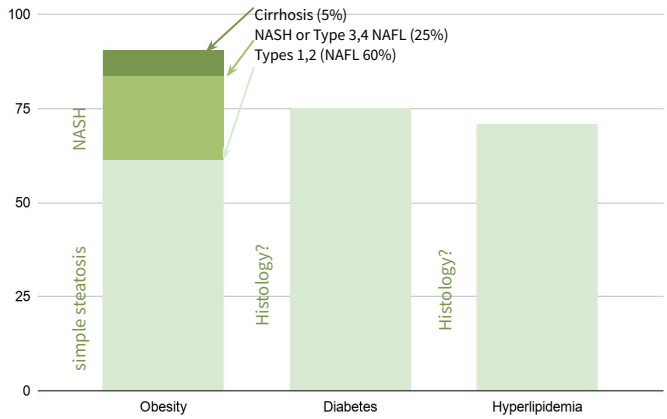


- **One billion** individuals worldwide have NAFLD.
- **Most common cause of abnormal liver tests**
- **Most common cause of chronic liver disease.**
- The **second leading etiology of liver disease among adults awaiting liver transplantation** in many countries (expected to be number one).
- Patients with NAFLD have **increased overall mortality** compared to matched control populations without NAFLD.[1]
- The frequency of steatosis varies with ethnicity (45% in Hispanics, 33% in whites and 24% in blacks) and gender (42% white males versus 24% white females) but only a minority of patients will progress to cirrhosis and end-stage liver disease.

◀ Global epidemiology of NAFLD: NOT IMP

- Global prevalence of NAFLD prevalence was 21.3% (17.9%- 30.5%); =20%
- NASH was prevalent in 26.2% of NAFLD patients

Prevalence is Higher in Risk Groups:



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%)**

NAFL 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%

1- Overall 33.2% risk of death or liver transplantation was observed, with liver-related mortality being the third most common cause of death after cardiovascular disease and extrahepatic malignancy.

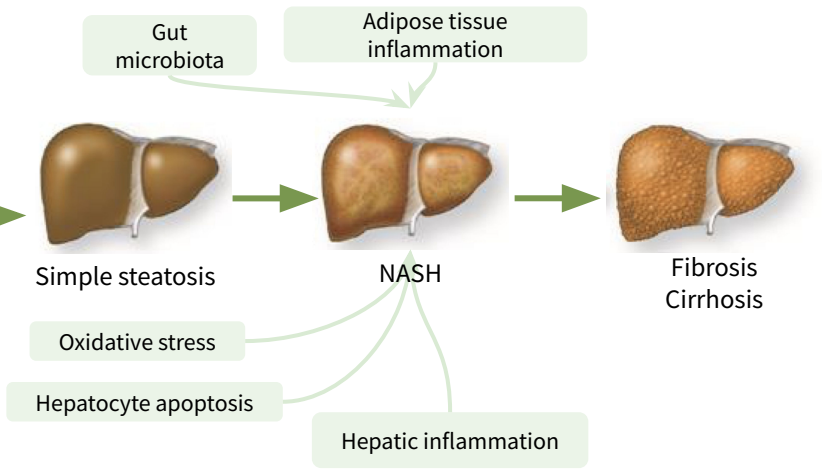
Pathogenesis and Natural History of NAFLD

◀ Pathogenesis of NAFLD

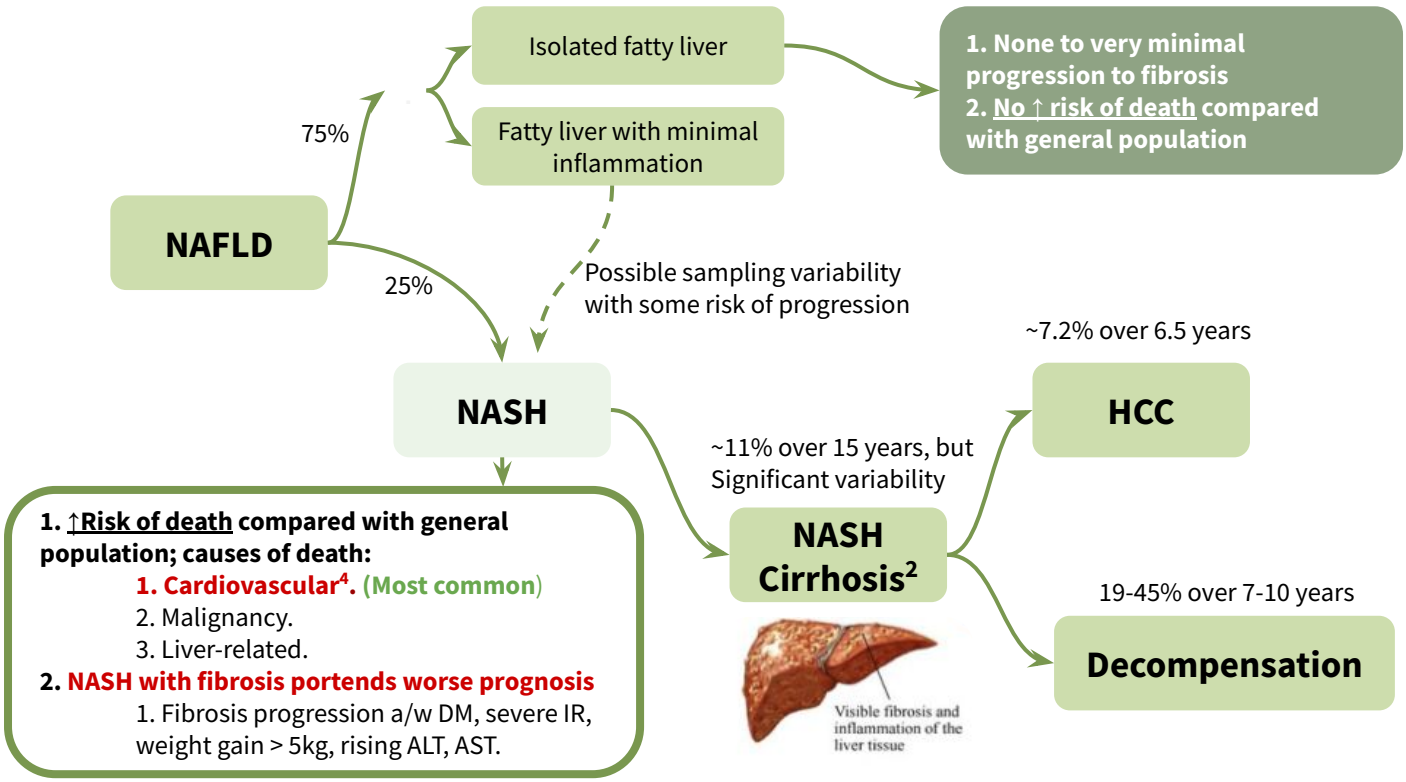
- The initiating events in NAFLD are based on the development of **obesity** and **insulin resistance**, leading to increased hepatic free fatty acid flux. This imbalance between the rate of import/synthesis and the rate of export/catabolism of fatty acids in the liver leads to the development of steatosis.[1]
- This may be an adaptive response through which hepatocytes store potentially toxic lipids as relatively inert triglyceride.
- **Overview:** The phases of fat accumulation and inflammation are overlapping. There is fat accumulation due to high fructose intake (de novo lipogenesis) + insulin resistance + other factors (eg, mitochondrial dysfunction, etc) → Hepatic Triglyceride accumulation → Lipotoxic effect with the release of many cytokines & inflammatory markers. This is also driven by many factors (eg, Gut microbiota).

Insulin resistance is the first step in most.
Insulin resistance leads to:
- ↑ lipolysis → FFA
- ★ ↑ hepatic uptake of free fatty acids (FFA) and accumulation of hepatic triglyceride.
- ★ De novo lipogenesis (eg, excess fructose[3])

→ Accumulation of hepatic triglycerides



◀ Natural History of NAFLD ★



1- This should not be confused with acute fatty liver, which can occur in hepatic mitochondrial cytopathies, e.g. acute fatty liver of pregnancy, or in other situations, e.g. Reye's syndrome or drug toxicity (sodium valproate, tetracyclines), or with bacterial toxins (e.g. Bacillus cereus). In these, defective mitochondrial beta-oxidation of lipids leads to fat droplet accumulation in hepatocytes and microvesicular steatosis

2- It is important to note that **hepatic fat content tends to diminish as cirrhosis develops** and so NASH is likely to be under-diagnosed in the setting of advanced liver disease, where it is thought to be the underlying cause of 30–75% of cases in which no specific aetiology is readily identified (so-called **'cryptogenic cirrhosis'**).

3- The only place to deal with fructose is the liver.

4- It is mainly due to the accompanying comorbidities, not the liver it self.

Evaluation of patient with NAFLD

History & Symptoms

Most are asymptomatic[2] (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

Exclude other causes of fatty liver

- **Alcohol**, medications
- HCV, HBV, HIV, autoimmune, Wilson
- Stigmata of liver disease

Identify at risk population

- Obesity, diabetes, dyslipidemia
- Metabolic syndrome (MS)
- Hypertension
- Ethnicity (Asians, hispanics)

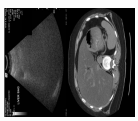
Physical examination & Imaging

Physical examination

As any other liver disease

1) Abdominal obesity
2) Enlarged liver
3) Signs of cirrhosis/ decompensation

Imaging[3]



Ultrasound[1,5] of abdomen:

- Enlarged liver
- Increase echogenicity (**bright**)

- CT (hypodense), MRI, MR spectroscopy,
- Elastrography

Laboratories

- Consistent with metabolic syndrome
- **LFT[1]:**
  - Normal[4] (in most of the cases)
  - **OR** Elevated bilirubin, AST, ALT[6], AP, GGT

Click here to check NFS and FIB-4 scores (EXTRA!!)

- Hepatic panel, Albumin, INR, platelets
- Emerging noninvasive panels (NAFLD fibrosis score, ELF score, APRI, BARD, FIB-4)

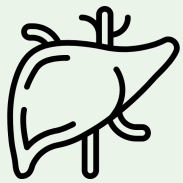
1- **BEST INITIAL: Liver function test (LFT) & Ultrasound and GOLD standard is Liver biopsy**
2- It is commonly identified as an **incidental** biochemical abnormality during routine blood tests or as a fatty liver during an ultrasound or CT scan of the abdomen. Alternatively, patients with progressive NASH may present late in the natural history of the disease with complications of cirrhosis and portal hypertension, such as variceal haemorrhage, or with hepatocellular carcinoma.
3- **No** routine **imaging modality can distinguish simple steatosis from steatohepatitis** or accurately quantify hepatic fibrosis short of cirrhosis.
4- Raising Liver enzymes indicates NASH, **But keep in mind there might be changes at the histological level without raising in the enzymes!**
5- **The sensitivity of Ultrasound is very low incase the liver fat is <20%**
6- ALT levels fall as hepatic fibrosis increases and the characteristic AST : ALT ratio of < 1 seen in NASH reverses (AST : ALT > 1) as disease progresses towards cirrhosis, meaning that steatohepatitis with advanced disease may be present even in those with normal-range ALT levels.

Evaluation of patient with NAFLD

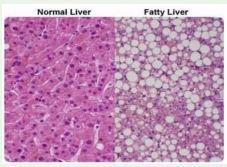
◄ Fibrosis assessment

Degree of fibrosis is the most important factor in prognosis

1) **Non-invasive methods**
   - Liver elasticity (e.g fibroscan)
   - Non-invasive serum markers scores



2) **Liver biopsy (Gold standard for DIAGNOSIS OF NASH)**[1]
   - **Confirm diagnosis** and **fibrosis stage**
   - Determine disease activity Fibrosis: stage
   - Exclude other diagnosis (when there is possibility of existence of other liver disease)
   - Not needed routinely



NAFLD Management

Targets

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

2) **Mange other Associated metabolic disorders**
   - Obesity, insulin resistance, DM & hyperlipidemia.

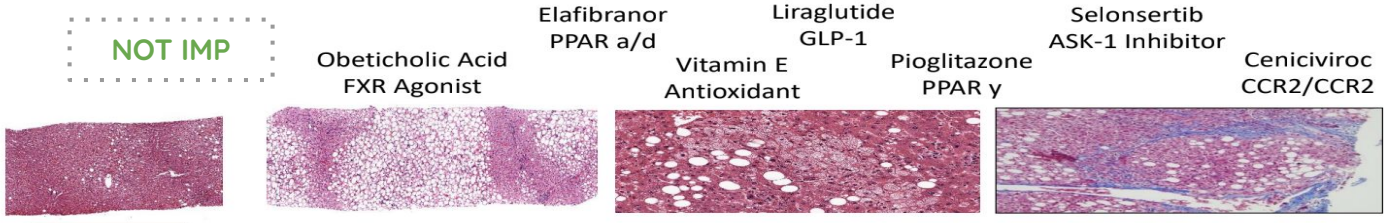
1. Pharmacologic Therapy

➔ **NO FDA approved drug for NASH, Why? because they do not affect the fibrosis.** "remember fibrosis is the most important prognostic factor"

➔ **Treatment directed at coexisting metabolic disorders:**
- To improve insulin sensitivity (with Glitazones), treat dyslipidemia (with Statins) and HTN
- Reduce oxidative stress effect
- Stop/slow necro-inflammation/fibrosis
- Improve underlying metabolic syndrome

Timing of Drug Action

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



Normal Liver → **Steatosis** → **Inflammation/ Apoptosis** → **Fibrosis**

1- The **histological definition** of NASH is based on a combination of three lesions (**steatosis**, **hepatocellular injury** and **inflammation**) with a mainly centrilobular, acinar zone 3 distribution.

NAFLD Management (cont.)

2. Lifestyle modifications (Most important)

- **Cornerstone Management.**
- **The only intervention with established evidence suggesting it is benefit and safety** with a clear dose-response association regardless the type of exercise.
- **Should be recommended as the primary intervention for NAFLD; includes:**
  - *Weight loss*, *Exercise* & *Dietary modification*.
- **These three interventions are more important than any medication. Weight loss is the most important one.**
- **Other measures:** Stop alcohol (for those who drink) and Treat other conditions (DM, Hyperlipidemia, etc..)

1 Weight Loss | 2 Dietary Composition | 3 Physical Activity

Strength of evidence

1) Weight Loss:

Weight loss[1] reduces associated risk factors, Consistently beneficial if sustained[2].

- ≥ 5% weight loss improves **Steatosis**.
- ≥ 7% weight loss improves **NASH**.
- ≥ 10% weight loss regress **Fibrosis**.

2) Dietary Composition

Beneficial without weight loss.

- **Low glycemic food.**
- Increased mono & polyunsaturated.
- **Avoid of high fructose containing food.**

▶

- Reduce liver fat.
- NASH and fibrosis (some evidence).
- Reduce risk for HCC.

3) Physical Activity

Aerobic & Resistance activity independently:

- Reduce liver fat.
- NASH and fibrosis (little evidence).

1. Orlistat, an enteric lipase inhibitor causing malabsorption of dietary fat, is used with a low-fat diet as an adjunct in subjects with a body mass index (BMI) of more than 30kg/m^2. Only those achieving a loss of body weight of more than 5% in 3 months should continue orlistat, and then for only 1 year, as fat-soluble vitamin deficiency may occur.

2. Sustained weight reduction of 7–10% is associated with significant improvement in histological and biochemical NASH severity.

NAFLD Management (cont.)

3. Other interventions

Intervention	Indication	Concerns
Bariatric surgery[1]	**Obese individuals** with NAFLD or NASH. Considered as another way of weight reduction, **Benefits**: • Resolution of steatosis. • Resolution of NASH. • Resolution of fibrosis (in some) • Improve other comorbidities, e.g DM	
Vit E	Biopsy-proven NASH, **Non-diabetic** (Discuss benefits and risks)	- Mortality[2]. - Hemorrhage. - Prostate cancer.
Pioglitazone	Biopsy-proven NASH with • **Diabetics** • Non Diabetics (Discuss benefits and risks)	- Weight gain. - Osteoporosis. - Bladder cancer.
Obeticholic acid	Still further data needed.	- Increase cholesterol. - Rebound weight gain.
Liraglutide	For **DM patients** No enough data to recommend.	
Metformin/ Ursodeoxycholic acid / Omega FA	Not recommended.	

- The best thing is to reduce the body weight, **first** by lifestyle modification then through the other methods (either pharmacological or Bariatric surgery)
- **Diabetics:** Pioglitazone or Liraglutide
- **Non-diabetics:** Vit E

Dr notes

Take home messages

- The disease spectrum ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), with or without fibrosis and can progress to cirrhosis.
- The presentation is variable from asymptomatic patient to liver cirrhosis with decompensation.
- Diagnosis based on radiology and non-invasive tests and sometimes liver biopsy is needed
- Treatment based mainly of life style modification (weight reduction with diet and exercise)
- No approved drugs for treatment of NASH

1. should be avoided in those with **advanced cirrhosis** and **portal hypertension**, but gastric bypass and sleeve gastrectomy have been shown to achieve weight loss and improve obesity-related co-morbidities in Child-Pugh A cirrhotic patients.
2. a meta-analysis showed an increase in all-cause **mortality** at doses over 400 IU/day, and an increased risk of **haemorrhagic** stroke and **prostate cancer** has also been reported.

Summary

Definition/ Classification	Liver disease, where there is accumulation of excess fat in the liver cells (steatosis), in people who drink little or no alcohol. **NAFL: Steatosis without inflammation**. **NASH: Steatosis with Inflammation.**
Criteria	1. Liver fat > 5%: Histology or MRI. 2. Lack of secondary causes (**NASH is a diagnosis of exclusion**).
Epidemiology	- One billion people have it worldwide. - Most common cause of abnormal liver tests and chronic liver disease.
Risk Factors	**Metabolic syndrome**, Insulin resistance (& T2DM), Central obesity, Hyperlipidemia, Male & Sedentary lifestyle.
Pathophysiology	Insulin resistance > ↑ Peripheral lipolysis, ↑ Triglyceride synthesis & ↑ Hepatic uptake of fatty acids.
Natural History	NAFLD $\rightarrow^{25\%}$ NASH $\rightarrow^{11\%}$ NASH Cirrhosis $\rightarrow^{7.2\%}$ HCC / $\rightarrow^{19\text{-}45\%}$ Decompensation.

Therapeutic modalities

1) Pharmacologic Therapy	**NO FDA approved drug**	➔ Stop/slow necro-inflammation/fibrosis ➔ Improve underling metabolic syndrome	➔ To improve insulin sensitivity ➔ Reduce oxidative stress effect
2) Lifestyle modifications **Cornerstone Management**	Should be recommended as the primary intervention for NAFLD: includes weight loss, exercise & dietary modification. Other measures: - Stop alcohol (for who drink) - Treat other conditions (DM, Hyperlipidemia, etc..)		
	Weight Loss: (reduce associated risk factors) Consistently beneficial if sustained. • ≥ 5% weight loss Steatosis. • ≥ 7% weight loss NASH. • ≥ 10% weight loss Fibrosis. **The only intervention with established evidence suggesting it is benefit and safety with a clear dose-response association regardless the type of exercise.**	**Dietary Composition:** - low glycemic food. - increased mono & polyunsaturated. - Avoid of high fructose containing food). Beneficial without weight loss. - Reduce liver fat. - NASH and fibrosis (some evidence). - Reduce risk for HCC.	**Physical Activity:** Aerobic & Resistance activity independently: - Reduce liver fat. - NASH and fibrosis (little evidence).

Intervention	Indication	Concerns
Bariatric surgery	Obese individuals with NAFLD or NASH. Considered another way of weight reduction, **Benefits**: - Resolution of steatosis. - Resolution of NASH. - Resolution of fibrosis (in some) - Improve other comorbidities, e.g DM	
Vit E	Biopsy-proven NASH, Non-diabetic (Discuss benefits and risks)	- Mortality. - Hemorrhage. - Prostate cancer.
Pioglitazone	Biopsy-proven NASH with or without DM (Discuss benefits and risks)	- Weight gain. - Osteoporosis. - Bladder cancer.
OCA	Still further data needed.	- Increase cholesterol. - Rebound weight gain.
Liraglutide	No enough data to recommend.	
Metformin/ UDCA/ Omega FA	Not recommended.	

Lecture Quiz

Q1: A 45-year-old man comes to the physician for a routine health maintenance examination. He feels well. He has type 2 diabetes mellitus. There is no family history of serious illness. He works as an engineer at a local company. He does not smoke. He drinks one glass of red wine every other day. He does not use illicit drugs. His only medication is metformin. He is 180 cm (5 ft 11 in) tall and weighs 100 kg (220 lb); BMI is 31 kg/m2. His vital signs are within normal limits. Examination shows a soft, nontender abdomen. The liver is palpated 2 to 3 cm below the right costal margin. Laboratory studies show an aspartate aminotransferase concentration of 100 U/L and an alanine aminotransferase concentration of 130 U/L. Liver biopsy shows hepatocyte ballooning degeneration, as well as inflammatory infiltrates with scattered lymphocytes, neutrophils, and Kupffer cells. Which of the following is the most likely diagnosis?

A- Primary biliary cirrhosis
B- Alcoholic fatty liver disease
C- Viral hepatitis
D- Nonalcoholic steatohepatitis

Q2: In most patients with NAFLD, the first step in the pathogenesis is:

A- Increase LDL
B- Increases TGs
C- Insulin resistance
D- Increased hepatic uptake of FFAs

Q3: What is the gold standard in the diagnosis of NASH?

A- Liver Elasticity (fibroscan)
B- Biopsy
C- Serum Markers
D- Liver MRI

Q4: Which of the following interventions has established evidence for the treatment of NAFLD?

A- Weight Loss
B- Orlistat
C- Metformin
D- Liraglutide

Q5: Which one of the following statements regarding non alcoholic fatty liver disease (NAFLD) is false?

A- Weight loss improves liver biochemistry
B- Liver biopsy should be considered in patients with diabetes or age >45yrs
C- Insulin resistance is almost universal
D- Cirrhosis develops in almost 40% of patients of NASH
E- Prevalence of NAFLD is up to 30% whereas prevalence of NASH is only up to 6%

Q6: Bariatric surgery can improve NASH, but rarely results in total resolution.

A- True
B- False

Q7: 14 year old African-American young woman is referred for evaluation of asymptomatic elevation of serum transaminases. She has not received blood transfusions. She is not taking medications. Examination shows that her body mass index is 34. She is anicteric and has no signs of portal hypertension but has prominent acanthosis nigricans in her neck folds and axilla.

Laboratory evaluation:

Hepatitis B surface Antigen	Negative	AST	100 IU/l
Hepatitis B surface antibody	Positive	ALT	120 IU/
Hepatitis C antibody	Negative	Total serum bilirubin level	0.4 mg/dl
		Serum immunoglobulin level	Normal

If a liver biopsy were performed, the most probable histologic findings would be:

A- Mixed portal infiltration with necrotic hepatocytes at the limiting plate
B- Macrovesicular hepatic steatosis with mild portal inflammation
C- Microvesicular hepatic steatosis
D- Cirrhosis with portal inflammation and Mallory bodies
E- Normal histology

Answers: Q1:D | Q2:C | Q3:B | Q4:A | Q5:D | Q6:B | Q7:B

Answers Explanation File!

THANKS!!

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Send us your feedback:
We are all ears!