



## **Pathophysiology-LIVER DISEASES**

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what is  
**Liver**  
**functions** ?

1. Gluconeogenesis, lipogenesis, protein metabolism, and storage of glycogen.
2. Conversion of ammonia to urea (urea cycle).
3. Synthesis of cholesterol, bile salts, albumin, angiotensinogen, plasma proteins, and clotting factors.
4. Activation and storage of vitamins such as vitamin D, A, K, E, and B12. in addition to copper and iron.
5. Metabolism of xenobiotics, toxins, and drugs by CYP450 in the smooth endoplasmic reticulum.
6. Conjugation and excretion of bilirubin

الخلاصة الامتحانية:

الكبد عضو **metabolically versatile**

و**biosynthetically indispensable**, لذلك

مرضه يضرب:

- الاستقلاب
- التخثر
- التخلص من السموم
- إفراز الصفراء
- توازن السوائل

# Liver injury

- As the major drug-metabolizing and detoxifying organ in the body, the liver is subject to injury from an enormous array of therapeutic and environmental chemicals.

كيف يصير الضرر؟

①

②

يعني المادة صارت لها قوة بين الخلية تحولها الى active toxic metabolite

- Injury may result from **direct toxicity**, through **hepatic conversion of a xenobiotic to an active toxin**, or by **immune mechanisms**, such as a drug or a metabolite which as a hapten to convert a cellular protein into an immunogen.

# Liver disease

The most important agent that produces toxic liver injury is **alcohol**; its characteristic histologic (but not clinical) features are shared with nonalcoholic fatty liver disease (NAFLD).

**Drug-induced liver disease** is a common condition that may manifest as a **mild reaction** or, much more seriously, as **acute liver failure** or **chronic liver disease**.

A large number of drugs and chemicals can produce liver injury.

مصادر سُمية أُخرى (مثل فطر أدوية)

Exposure to other potential toxins such as **herbal remedies**, **dietary supplements**, **topical applications** (e.g., ointments, perfumes, shampoo), and **environmental exposures** (e.g., Cleaning solvents, pesticides, fertilizers).

# Liver disease

تصيب معظم الناس  
dose-dependent  
يعني كلما زاد الجرعة زاد الضرر

لا تصيب الجميع  
تختلف كل على  
individual host variations  
مثلاً في الاستجابة للجسم  
في سرعة امتصاص الدواء  
و في معدلات التمثيل  
يعني لو أخذوا نفس الجرعة  
وتمتصها في وقت واحد

- Drug reactions may be classified as **predictable or unpredictable (idiosyncratic)**.
- Predictable drug or toxin reactions **affect all people in a dose-dependent fashion.**
- Unpredictable reactions depend on **individual host variations**, particularly the **propensity to mount an immune response to drug-related antigen** or the **rate at which the agent is metabolized.**
- Both classes of injury may be immediate or take weeks to months to develop.

النوعين يمكن يكونوا immediate  
بعض أسابيع أو أشهر عتبات فيسفر

predictable = dose-related

idiosyncratic = person-related

شوا أصناف آرام الكبد؟

# Different Forms of Hepatic Injury

أدوية مرتبطة

أدوية مرتبطة

- Pattern of injury and associated agent
  - ① ✓ **Cholestasis (as a decrease in bile flow)**
    - Contraceptive and anabolic steroids; estrogen replacement therapy
  - ② ✓ **Cholestatic hepatitis (inflammation of the liver)**

يعني عن الـ Cholestasis مع Inflammation

    - Numerous antibiotics; phenothiazines
  - ③ ✓ **Hepatocellular necrosis**

موت خلايا الكبد

    - Methyldopa, phenytoin
    - Acetaminophen, halothane
    - Isoniazid, rifampicin

أدوية مرتبطة

# Different Forms of Hepatic Injury

تراكم الكحول داخل الكبد

④ ✓ Steatosis (accumulation of fat in the liver)

• Ethanol, methotrexate, corticosteroids, total parenteral nutrition

أدوية

⑤ ✓ Steatohepatitis (fatty liver disease, characterized by inflammation of the liver with concurrent fat accumulation in liver)

inflammation + steatosis  
التهاب + تراكم

• Amiodarone, ethanol

أدوية

⑥ ✓ Fibrosis and cirrhosis (damage of hepatocytes which form scary lesion in the liver instead)

الخلايا تتأذي ويستعمل النسيج الضام  
scar tissue

• Methotrexate, isoniazid, enalapril

أدوية

⑦ ✓ Vascular lesions

أضرار وعائية

• oral contraceptives, tamoxifen

هون كلسم أورام ( Cancer )

# Different Forms of Hepatic Injury

8 ✓ Neoplasms (benign tumor formed from glandular structures in epithelial tissue)

- Hepatic adenoma ( oral contraceptives, anabolic steroids)

9 ✓ Hepatocellular carcinoma.

سرطان الخلايا الكبدية

10 ✓ Cholangiocarcinoma (bile duct cancer, is a type of cancer that forms in the bile ducts)

سرطان القنوات الصفراوية

11 ✓ Angiosarcoma (cancer in the blood vessel wall) (vinyl chloride)

سرطان ينشأ من جدار الأوعية الدموية

نكح أدمعج

How

- Jaundice results from the retention of bile.
- Hepatic bile formation serves two major functions. First, bile constitutes the primary pathway for the elimination of bilirubin, excess cholesterol, and xenobiotics that are insufficiently water soluble to be excreted in the urine.
- Second, secreted bile salts and phospholipid molecules promote emulsification of dietary fat in the lumen of the gut.
- Bile formation is a complex process and is readily disrupted by a variety of hepatic insults.

excretory pathway

يعني تفتت الدهون داخل الأمعاء لتسهيل هضمها وامتصاصها

# Jaundice and Cholestasis



## MAIN CAUSES OF JAUNDICE:

☐ Predominantly unconjugated hyperbilirubinemia.

Excess production of bilirubin.

فیبیا تکلیسر RBCs اُسریج منہ تہینیکہ ← Hemolytic anemias (a disorder in which red blood cells are destroyed faster than they can be made).

یعنی اڈانجم دم داخای شم تملل ← Bilirubin ↑ Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas).

Ineffective erythropoiesis syndromes (e.g., Pernicious anemia, Thalassemia)

Impaired bilirubin conjugation

Physiologic jaundice of the newborn

# Cholestasis:

② Results from impaired bile flow due to hepatocellular dysfunction or intrahepatic or extrahepatic biliary obstruction, also may manifest as jaundice. ①

- However, sometimes *pruritus* is the presenting symptom the pathogenesis of which remains obscure. ③

④ *Skin xanthomas* (focal accumulations of cholesterol) sometimes appear, the result of hyperlipidemia and impaired excretion of cholesterol.

ترسبات کو لیسنترول فی  
الجلد بسبب

- 1- higher lipidemia
- 2- impaired cholesterol excretion

## □ A characteristic laboratory finding is :

- *Elevated serum alkaline phosphatase*, an enzyme present in bile duct epithelium and in the canalicular membrane of hepatocytes.
- A different alkaline phosphatase isozyme normally is expressed in many other tissues such as bone, and so hepatic origin must be verified.
- Reduced bile flow causes intestinal malabsorption including inadequate absorption of the fat-soluble vitamins A, D, and K.

Clothing  
Factors

نقص  $\star$  vitamin k  
عوامل النزف الاله يوضري كالي

# Hepatitis

- Means inflammation of the liver.
- Can be caused by:
  - ✓ Genetic diseases (metabolic disorders)
  - ✓ Medications (including over-the-counter)
  - ✓ Alcohol
  - ✓ Autoimmune disease
  - ✓ Obesity
  - ✓ Hepatitis viruses (A,B,C,D,E)

Hepatitis can heal on its own with no significant consequence, or it can progress to scarring of the liver. Acute hepatitis lasts under **six months**, while chronic hepatitis lasts longer.

Acute  $\leq$  6 months      chronic  $>$  6 months

عقو بيشنضى لجاله  
أويستظور ابي scarring  
شم هرين هزومت

# Acute symptomatic Hepatitis- Clinical manifestation

مرحلة قبل ظهوره

## □ Preicteris phase:

- General malaise, <sup>توعاض عام</sup> myalgia, <sup>ألم عضلات</sup> arthralgia, <sup>ألم مفاصل</sup> easy fatigability, <sup>فقدان الشهية حاد</sup> severe anorexia.
- Nausea, vomiting and diarrhea or constipation may occur.
- Mild abdominal pain is felt in the right side.
- Chills and fever.
- Smokers will have a distaste for smoke.
- AST and ALT show variable increases.

# Acute symptomatic Hepatitis- Clinical manifestation

تأتي بعد المرحلة الأولى من 5-10 أيام

## □ Icteric phase:

- After 5-10 days of preicteric phase.
- Onset of Jaundice followed by progressive following improvement يميزه Jaundice ثم يتحسن المريض تدريجياً
- Severe pruritis (because of bile salts) and liver tenderness are common features.

## □ Convalescent phase: مرحلة النقاهة تحسن الإحساس العام / رجوع الشهية / اختفاء ال Jaundice

- Increase sense of well-being, return to appetite, and disappearance of jaundice.
- Complete recovery by about 9 weeks in hepatitis A and 16 weeks of uncomplicated hepatitis B.

المرحلة بمرتب 3

p for drom.c → Jaundice → recovery

# Hepatitis- Viral hepatitis

- Hepatitis is a viral infection that causes inflammation of the liver.
- There are five main types of viral hepatitis: A, B, C, D, E.
- Hepatitis A and E are typically caused by ingestion of contaminated food or water. *Facial-oral transmission*
- Hepatitis B, C and D are typically caused by contact with contaminated blood or body fluids.
- In particular viral hepatitis types <sup>نحو انتقالها؟</sup> B and C lead to  
① chronic disease in hundreds of millions of people and, together, are the most common cause of liver  
② cirrhosis and cancer. ③
- About 1 million people die each year from causes related to viral hepatitis.

A, E = Acute

D, C, B = chronic

# Viral hepatitis

- Hepatitis B and C cause a high burden of disease.
- Only 1 in 5 persons exposed to the hepatitis B and C virus develops acute symptoms, but chronic infection is common.
- Co-infection of HCV and HIV is common, especially among people who inject drugs.
- Presented as acute asymptomatic, symptomatic, or chronic disease (carrier state).
- May develop to fulminant hepatic failure (hepatic insufficiency with rapid progression to liver failure (hepatitis B)).

خاصة في B hepatitis  
يعني فشل كبدي سريع وشديد rapid  
⇒ progression to liver failure

# Viral hepatitis

(Modes of Transmission)

HBV/HCV = Parental + blood + body fluid

HAV/HEV = Fecal-oral

## Hepatitis B virus (HBV):

- Sexual contact.
- Mother-to-child transmission.
- Blood-to-blood contact by unsafe injecting practices, blood transfusion, unsterile medical equipment (HBV is an important occupational hazard for health workers)

## Hepatitis C virus (HCV):

- Blood-to-blood contact by unsafe injecting practices (main transmission mode in the WHO European region), blood transfusion, unsterile medical equipment.
- Sexual contact (less common).

Top F ← HBV and HCV are many more times more infective than HIV

# Viral hepatitis Prevention

- Promote vaccination against hepatitis B.
- Ensure needle and syringe programs to avoid sharing injecting equipment.
- Promote safe sex.
- Ensure adequately sterilized medical equipment.
- Promote hepatitis B and C testing and counseling services.
- Raise awareness of the diseases and their transmission modes, especially among key populations.

طرق العلاج

# Viral hepatitis Treatment

- Usually, acute infection with hepatitis B or C does not require treatment.
- Combination antiviral therapy has been the mainstay of treatment for chronic hepatitis B and C.
- Treatment remains poorly accessible and too costly for many of those in need. Also, <sup>مشاكل العلاج</sup> poor response to the treatment, problems with adherence, and intolerance to the medicines result in low numbers of people in treatment.
- New and effective medications are becoming available.

Symptomatic, biochemical or serological evidence of continuing relapsing.

كيف يمكن ظهوره  
Can be only manifested by elevated liver enzymes and if symptoms appear, they include fatigue, abdominal discomfort and joint or muscle aches.

Only hepatitis B, C, and D may produce a carrier state but not A.

# Chronic hepatitis

# Test for hepatobiliary function

secretory function

Imaging

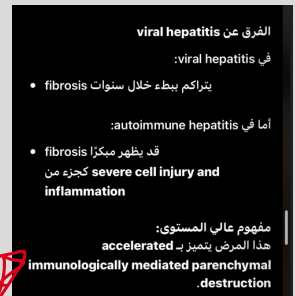
- Liver enzymes, ALT (liver-specific), and AST indicate acute hepatocellular injury as in viral hepatitis, autoimmune hepatitis, hypoxic injury, and acute toxic injury.
- Synthetic ability of the liver: *تسوية وظائف الكبد Liver*
  - ✓ Measure albumin level
  - ✓ Prothrombin time (clotting factors) (is a blood test that measures how long it takes blood to clot)
  - ✓ Serum bilirubin,  $\gamma$ -glutamyltransferase, and alkaline phosphatase measure hepatic secretory function (a sensitive indicator of hepatobiliary disease).
- Ultrasonography and CT-scan, for detection of stones in the gallbladder or biliary tree and blood and bile flow through the liver.
- Liver biopsy in introducing a fine needle to determine the stage of liver cancer.

ALT و AST على نسبه سكر و دهون + املاح

# Autoimmune Hepatitis

- Autoimmune hepatitis is a chronic disorder associated with histologic features that may be indistinguishable from chronic viral hepatitis.
- Female predominance (70%).
- Absence of serologic evidence of viral infection.
- Elevated serum IgG (levels greater than 2.5 g/dl).
- High titers of autoantibodies in 80% of cases.
- Although autoimmune hepatitis shares patterns of injury with acute or chronic viral hepatitis, the time course of histologic progression differs.
- In viral hepatitis, fibrosis typically follows years or decades of slowly accumulating parenchymal injury, whereas, in autoimmune hepatitis, it is an early phase of severe cell injury and inflammation.

دوره إندو الكبدية  
Autoimmune hepatitis  
عند



NonAlcoholic و Alcoholic  
الكبدية غير الكحولية والكبدية الكحولية

## ALCOHOLIC AND NONALCOHOLIC FATTY LIVER DISEASE

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- Alcohol is a well-known cause of fatty liver disease in adults and can manifest histologically as steatosis, steatohepatitis, and cirrhosis.

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-Nonalcoholic fatty liver disease (NAFLD), can mimic the entire spectrum of hepatic changes typically associated with alcohol abuse.

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-NAFLD is <sup>what</sup> associated<sup>?</sup> with <sup>①</sup> insulin resistance, <sup>②</sup> obesity, <sup>③</sup> diabetes mellitus, <sup>④</sup> hypertension, and <sup>⑤</sup> dyslipidemias (Metabolic syndrome).

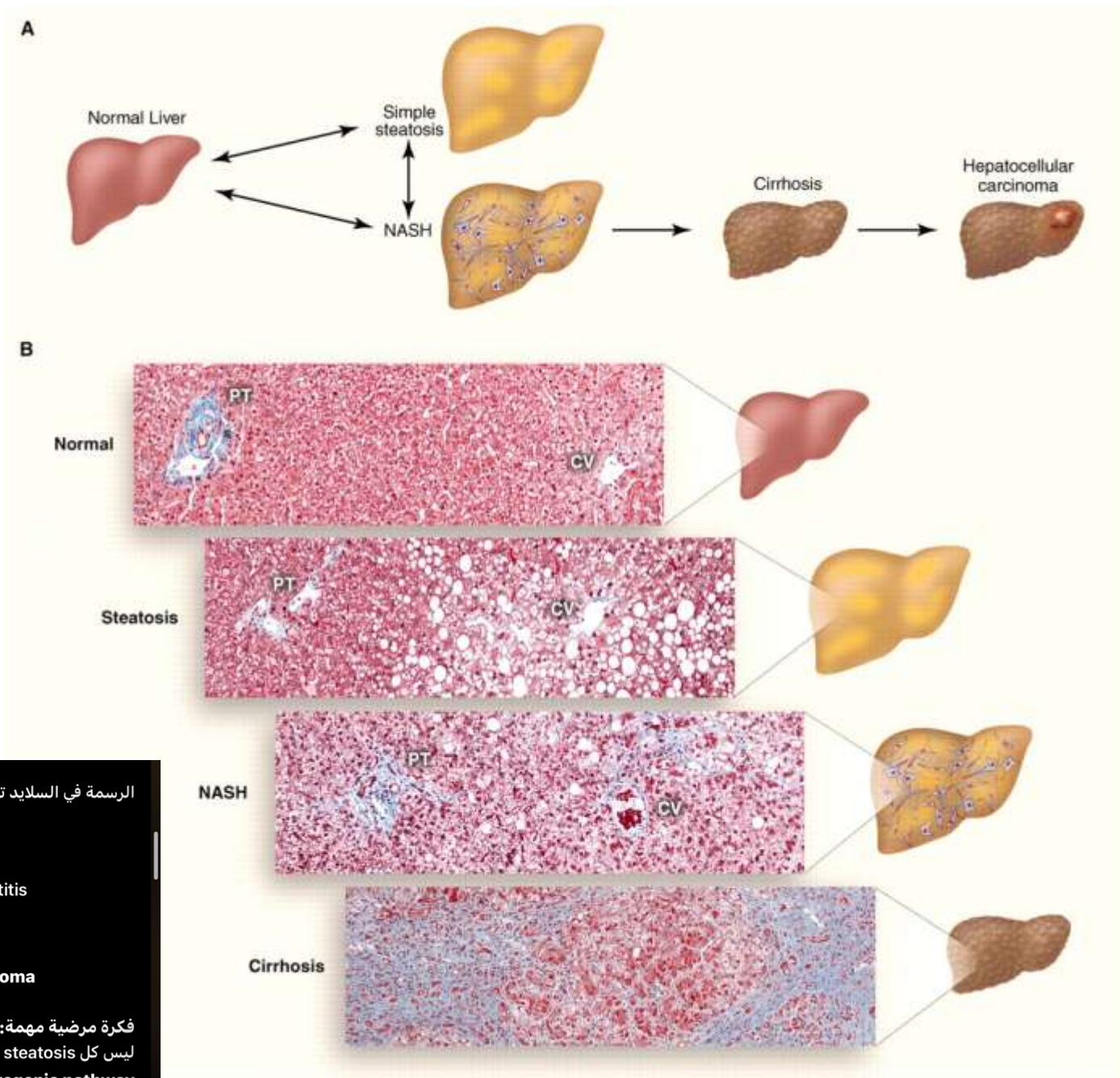
# MORPHOLOGY

• Three categories of liver alterations are observed in fatty Liver disease:

• Steatosis (Fatty change), تراكم الدهون

• Steatohepatitis. دهون + التهاب

• Fibrosis. تليف



الرسمة في السلايد توضح progression من:

- normal liver
- إلى simple steatosis
- إلى NASH / steatohepatitis
- إلى cirrhosis
- ثم قد يصل إلى hepatocellular carcinoma

فكرة مرضية مهمة:  
ليس كل steatosis يتطور، لكن إذا دخل في طور inflammatory fibrogenic pathway فقد ينتهي بتليف وتشمع.

# Alcoholic liver disease

- Excessive ethanol consumption causes more than 60% of chronic liver diseases in western countries and accounts for 40% to 50% of deaths due to cirrhosis.
- The following statistics attest to the magnitude of the problem in the united states:
- **More than 10 million Americans are alcoholics.**
- **Alcohol abuse is the fifth leading cause of death**, being responsible for 80,000 to 85,000 deaths annually.

Of these deaths, 20,000 are attributable directly to end-stage

Cirrhosis; another 10,000 to 12,000 are the result of automobile accidents.

# Alcoholic liver disease

- Consumption of 50 to 60 g/day of alcohol is considered to be the threshold for the development of alcoholic liver disease. Cirrhosis typically develops after 10 to 15 years of drinking. *gram/day = threshold*
- Ethanol is metabolized in the liver by two different pathways: alcohol dehydrogenase and microsomal ethanol-oxidizing system producing acetaldehyde in both pathways.
- NADH is produced by alcohol dehydrogenase. Fatty acid oxidation requires large quantities of NAD which was consumed during ethanol metabolism leading to the accumulation of fat in the liver.
- The multiple pathologic effects of alcohol include *what are* changes in lipid metabolism, decreased export of lipoproteins, and cell injury caused by reactive oxygen species and cytokines.

# Nonalcoholic Fatty Liver Disease (NAFLD)

- NAFLD is a common condition in which fatty liver disease develops in persons who do not drink alcohol.
- The liver can show any of the three types of changes described earlier (steatosis, steatohepatitis, and cirrhosis).
- NAFLD is consistently associated with insulin resistance and metabolic syndrome.

بہتر ہے

شوا الأثر مرافق الحماض

➤ **Other commonly associated abnormalities are:**

✓ **Type 2 diabetes** (or family history of the condition).

✓ **Obesity**, primarily central obesity (body mass index greater than 30 kg/m<sup>2</sup> in whites and greater than 25 kg/m<sup>2</sup> in Asians).

✓ **Dyslipidaemia** (hypertriglyceridemia, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol).

✓ **Hypertension.**

# Clinical Feature & diagnosis of NAFLD

المرض الأكثر شيوعاً



- ❖ NAFLD is the most common cause of incidental elevation of serum transaminases.
- ❖ Most persons with steatosis are asymptomatic; patients with active steatohepatitis or fibrosis may also be asymptomatic, but some may have fatigue, malaise, right upper quadrant discomfort, or more severe symptoms of chronic liver disease.
- ❖ Liver biopsy is required for diagnosis.
- ❖ Fortunately, the frequency of progression from steatosis to active steatohepatitis and then from active steatohepatitis to cirrhosis seems to be low.

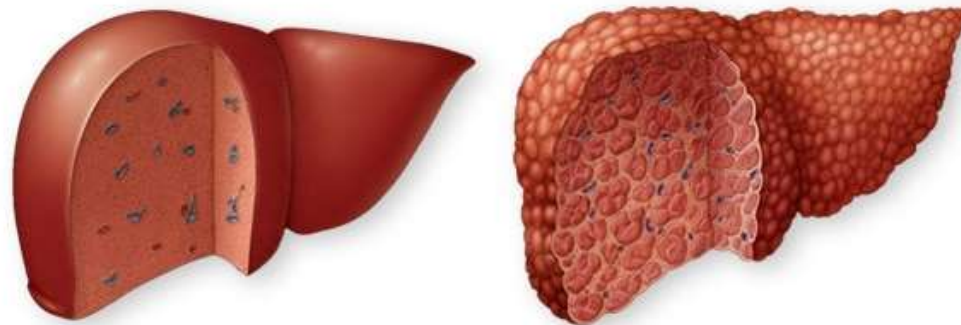
التحول من ->  
Steatosis → Steatohepatitis → Cirrhosis  
قليل من

- ❖ Nevertheless, NAFLD is considered to be a significant contributor to the pathogenesis of “cryptogenic” cirrhosis.
- ❖ Because they share common features, the incidence of coronary artery disease is increased in patients with NAFLD.   
 ← لايشي الكريفن عندو نضف  
الأعراض  
1-obesity  
2- insulin Resistance  
3- dyslipidemia
- ❖ Current therapy of NAFLD is directed toward obesity reduction and a decrease in insulin resistance.
- ❖ Pediatric NAFLD is increasingly being recognized as the obesity and metabolic syndrome epidemic spreads to pediatric age groups.

# Liver Cirrhosis

- Cirrhosis is among the top 10 causes of death in the western world.
- Cirrhosis is defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

Fibrosis  
تحويل البنية الطبيعية للكبد (Structurally abnormal nodules) ←  
تتكون بـ diffuse ←



# Symptoms

- **The most common side effects are:**
  - Weight loss.
  - Cachexia.
  - Weakness.
  - Anorexia.
  - Upper right abdominal pain.
  - Most of the times diarrhea and sometimes constipation.

# Late symptoms and complications

- **Portal hypertension:** disruption of the blood flow due to fibrosis leading to liver cell failure.
- **Splenomegaly:** shunting of blood into the splenic vein due to portal hypertension. This leads to the decreased life span of all blood elements leading to anemia, thrombocytopenia, and leukopenia.
- **Ascites:** few liters of fluids in the abdomen due to the increase in the hydrostatic pressure caused by portal hypertension, sodium, and water retention and decreased osmotic pressure due to decreased albumin synthesis. It can be treated by sodium restriction and diuretics.

Ascites

# Late symptoms and complications

- **Portosystem shunt** (esophageal and gastric varices, hemorrhoids) due to portal hypertension.
- **Bleeding** due to decreased clotting factors and thrombocytopenia due to splenomegaly.
- **Gynacomastia and testicular atrophy** due to the fall in testosterone levels.
- **Palmar erythema:** redness of the palm caused by increased blood flow.

# Late symptoms and complications

- **Hepatic encephalopathy:** lack of mental alertness, confusion, and coma. An early sign is a flapping tremor. Other signs include memory loss, anxiety, and speech impairment. Encephalopathy may progress to decerebrate rigidity and coma.
- **Hepatic failure:** sudden and massive liver destruction. 80-90% of the liver function must be lost before hepatic failure occurs. Liver failure results in GI bleeding, electrolyte disturbances, and heart failure.

علامات  
مبكرة

ممكن تتصور اني

# Thank You

الكبد الطبيعي يقوم بوظائف:

- metabolic
- synthetic
- detoxifying
- excretory

وعندما يتأذى بسبب:

- alcohol
- drugs
- viruses
- autoimmune causes
- obesity/metabolic syndrome

فإنه قد يمر بمراحل:

- hepatocellular injury
- cholestasis
- hepatitis
- steatosis / steatohepatitis
- fibrosis
- cirrhosis
- hepatic failure أو hepatocellular carcinoma ثم

وأهم النتائج السريرية:

- jaundice
- pruritus
- elevated enzymes
- portal hypertension
- ascites
- varices
- encephalopathy
- bleeding tendency