Liver Function

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Editing File

Objectives:

- Understand the major metabolic functions of the liver and causes of liver dysfunction.
- Discuss markers of liver function tests such as liver enzymes, bilirubin, albumin and prothrombin time that can diagnose hepatic injury and assess hepatic function.

And.....

the Liver

Major Metabolic Functions

Synthetic
- Triglycerides
- Cholesterol
- Lipoproteins
- Plasma proteins
  - Albumin.
  - Globulins.

Detoxification & excretion
- Bilirubin
- Cholesterol
- Drug metabolites
- Urea cycle

Ammonia → urea

Storage
- Vitamins
  - A.
  - D.
  - E.
  - K.
  - B_{12}.

Production
- Bile salts
  - Helps in digestion.

Examples of dysfunction

- **Hepatocellular disease**
- **Cholestasis** (obstruction of bile flow)
- **Hepatitis**
- **Steatosis** (fatty liver)
- **Cirrhosis**
- **Jaundice**
- **Liver cancer**
- **Genetic Disorders**
  - Hemochromatosis (iron storage).

Liver Function Tests (LFTs)

★ Noninvasive methods for screening of liver dysfunction.

1. Help in identifying general types of disorder
2. Assess severity & allow prediction of outcome
3. Disease & treatment follow up

★Classification

Markers of hepatic injury Mild or severe / acute or chronic		Markers of liver dysfunction
Hepatocellular	**Cholestasis** Or biliary obstruction	**Serum bilirubin** total (direct & indirect) & conjugated
Alanine aminotransferase **(ALT)**	Alkaline phosphatase **(ALP)** [1] → Infiltrative disease.[2]	**Urine** bile salts and urobilinogen
Aspartate aminotransferase **(AST)**	γ-glutamyltransferase **(GGT)** [3]	**Protein** ◆ Total. ◆ Serum albumin . ◆ Albumin/globulin ratio. ★ Synthetic function
	Bilirubin → Impaired conjugation ..	**Prothrombin Time** ★ Synthetic function
	Bile acids	

1. Related to the bones but was found in the membrane in hepatocytes
2. Infiltrative disease in which the liver is invaded or replaced by non-hepatic substance such as neoplasm.
3. important for detection of alcohol/ drug abuse

Liver Function Tests (LFTs)

Limitations

Normal values don't always indicate absence of disease

Liver has a very large reserve capacity

Asymptomatic people may have abnormal results

Diagnosis should be based on clinical examination[1]

Bilirubin

- A byproduct of RBC breakdown
- The yellowish pigment in jaundice

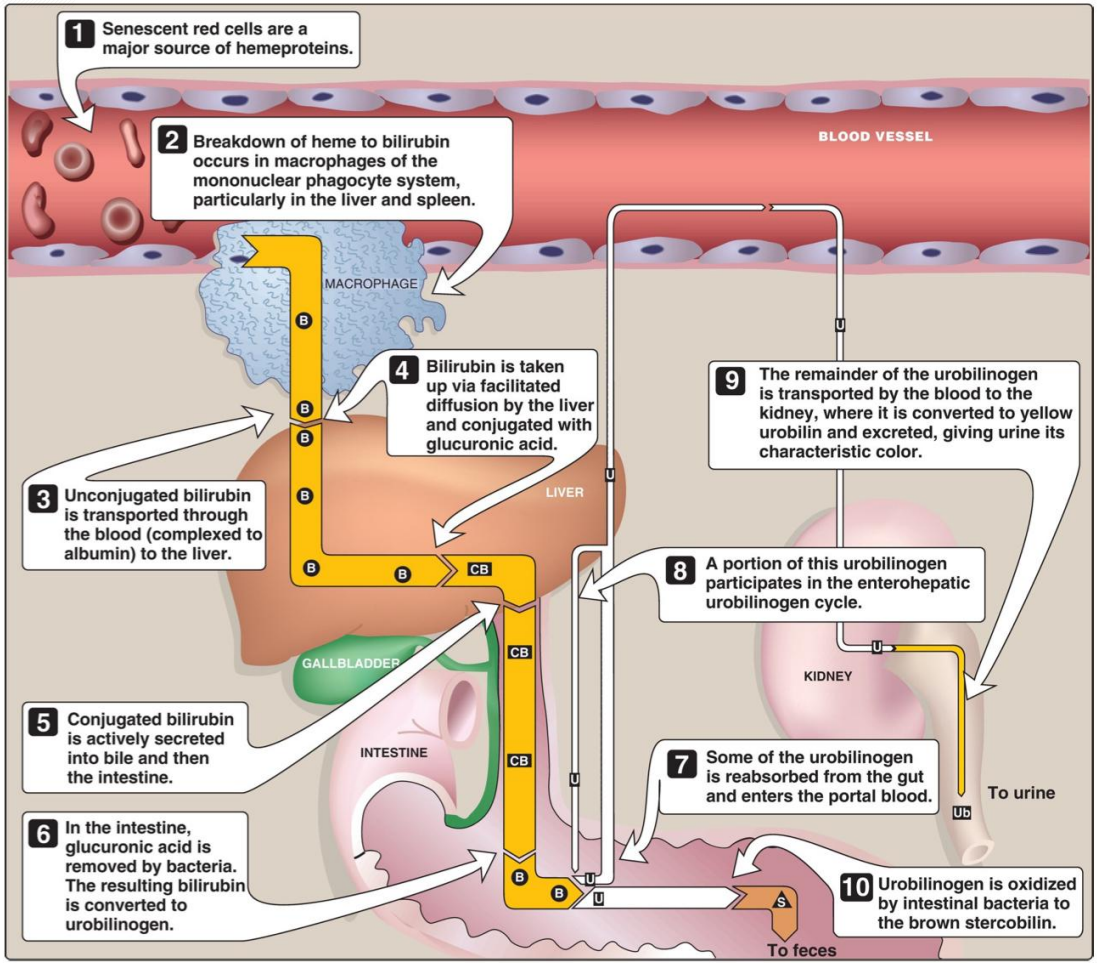
High levels are observed in :

1. Gallstones
2. acute & chronic hepatitis

Serum levels	
Normal	0.2 – 0.8 mg/dL
Unconjugated (indirect)	0.2 – 0.7 mg/dL
Conjugated (direct)	0.1 – 0.4 mg/dL
Latent jaundice	> 1 mg/dL less than 2 mg/dL
Jaundice	> 2 mg/dL

Jaundice	
Pre-hepatic (Hemolytic)	1- Abnormal RBCs 2- Antibodies 3- Drugs & toxins 4- Hemoglobinopathies (thalessemia) 5- Gilbert's syndrome [2] 6- Crigler-Najjar syndrome [2]
Hepatic (Hepatocellular)	1- Viral hepatitis 2- toxic hepatitis 3- intrahepatic cholestasis
Post-hepatic	1- Extrahepatic cholestasis 2- gallstones 3- tumors of the bile duct 4- carcinoma of the apex of pancreas

1. Remember that these tests aren't sensitive nor specific for liver disease
2. Varying degrees of deficiency of bilirubin UDP-glucuronosyltransferase result in Crigler-Najjar I and II and Gilbert syndrome, with Crigler- Najjar I being the most severe.



Explanation

1- Rupture of RBCs lead to release of heme

2- Heme is converted to biliverdin catalyzed by microsomal heme oxygenase which is reduced to bilirubin

3- bilirubin is complexed with albumin and released at entrance to the liver (unconjugated bilirubin).

4- Bilirubin is conjugated with UPD-glucuronic acid.

5- Conjugated bilirubin is secreted into bile and then into the intestine.

6- Bacteria utilize glucuronic acid so it remove it from bilirubin converting it into urobilinogen.

★ **Fate of urobilinogen:**

7- **Some enter the portal circulation where:**

8- Returns back to the liver.

9- filtered by the kidney as urobilin

10- **majority is excreted with feces as stercobilin** (gives the feces its characteristic color)

Markers for liver dysfunction

Marker	Urobilinogen	Bile salts	Serum albumin	Serum globulin	Prothrombin time
Normal levels	Most are metabolised in the large intestine, but a fraction is excreted in the urine: less than 4 mg/day	Normally not found in urine	3.5 - 5 g/dL (measured from the serum)	2.5-4.5 g/dL	
Features		Obstruction of biliary passages → leakage of bile salts into the circulation → excretion in urine	-The most abundant protein synthesized by the liver -Synthesis depends on the extent of functioning liver cell mass - Longer half life: 20 days	- α and β globulins are mainly synthesized in the liver - They constitute immunoglobulins (antibodies)	- Synthesized by the liver - Half life = 6 hours → indicates **present** function of the liver (an early marker)
In disease		**Excreted** in urine	**Low** in all chronic liver diseases	**High** serum γ-globulins in chronic hepatitis & cirrhosis: ➔ IgG: autoimmune hepatitis ➔ IgA: alcoholic liver disease	It is **prolonged** only when the liver loses more than 80% of its reserve capacity
Notes	Measured from **urine**		Albumin to globulin (A/G) ratio: - Normally: 1.2/1 - 1.5 /1 (1.2-1.5 albumin molecules for every 1 globulin) - Hypoalbuminemia: globulin levels increase as a compensation		- Vit. K also causes prolonged PT - Vit K intake does not affect PT in liver disease

Markers for hepatocellular injury

Marker	Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Normal levels	8-20 U/L	• Male: 13-35 • Female: 10 - 30
Features	Marker for hepatocellular damage	- More liver-specific than AST - Appears in plasma many days before clinical signs appear - Obese but otherwise normal individuals may have elevated ALT levels
In disease	**High** serum levels are observed in: • Chronic hepatitis • Cirrhosis • Liver cancer	➔ **Minor elevations** (50 - 100 U/L): ◆ cirrhosis ◆ hepatitis C ◆ non-alcoholic steatohepatitis (NASH) ➔ **Moderate elevations** (100 - 300 U/L): ◆ alcoholic hepatitis ➔ **High serum levels** (300 - 1000 U/L): ◆ acute hepatitis
Notes	Not very specific for liver disease; could be used as a marker for diseases in organs such as the heart, the brain, the kidney, skeletal muscles, bones	- If both AST + ALT were high → liver disease - If AST levels were much higher than ALT → could indicate basal muscle damage since it's also present in cardiac + skeletal muscles

Markers of cholestasis

Marker	Alkaline phosphatase (ALP)	ɣ Glutamyltransferase (GGT)
Normal levels	40 - 125 U/L	10 - 30 U/L
Features	- Non-specific marker of liver disease - Produced by bone osteoblasts (for bone calcification) + placenta[1] - Present on hepatocyte membrane	- Used for glutathione synthesis - Highly sensitive for alcohol abuse; it is **increased** in **alcoholics** despite normal liver function tests
In disease	➔ **Minor elevations** observed in: ◆ infective hepatitis ◆ alcoholic hepatitis ◆ hepatitis ◆ hepatocellular carcinoma ➔ **High elevations** observed in: ◆ Extrahepatic obstruction (obstructive jaundice) ◆ Intrahepatic cholestasis ➔ **Very high** levels observed in: ◆ Bone diseases[2]	➔ **Moderate elevations** observed in: ◆ Infective hepatitis ◆ Prostate cancers ➔ High in alcoholics
Notes	1. Could be high in pregnancy 2. Elevated alone, without GGT indicates bones disease → ALP + GGT are always measured together to indicate liver obstruction	Alcohol leads to liver damage and affects many parameters. However, since GGT is very sensitive to alcohol, it becomes elevated earlier than other enzymes

Take Home Messages

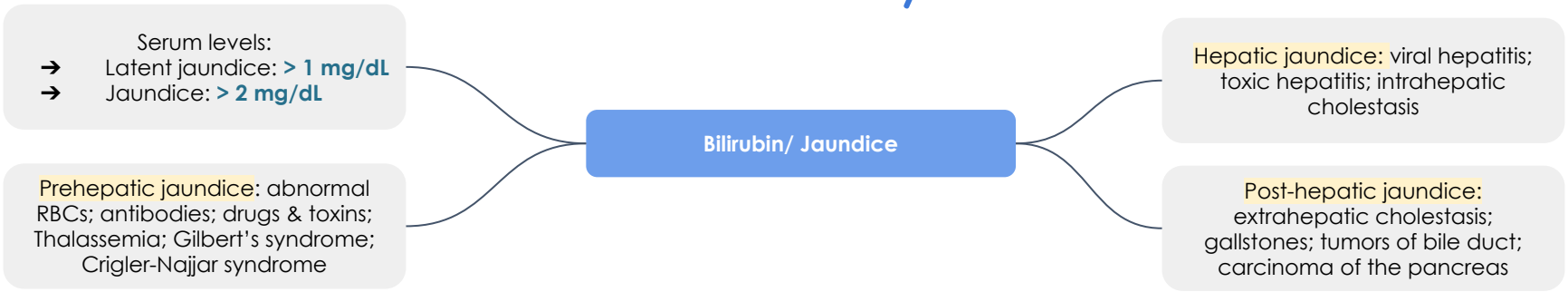
- **LFTs help detect liver injury and function**
- **LFTs do have some limitations**

Done studying? Let's see if your memory is still working!!

issa joke

CLICK ON ME!!

Summary



Marker	Bilirubin	Bile salts	Serum albumin	Serum globulin	Prothrombin time	AST	ALT	ALP	GGT
Change	↑	Excreted in urine	↓	↑	Prolonged	↑	↑	↑	↑
Disease	- Gallstones - Acute & chronic hepatitis	Biliary passage obstruction	All chronic liver diseases	Chronic hepatitis & cirrhosis: - IgG: autoimmune hepatitis - IgA: **alcoholic liver disease**	When the liver loses more than 80% of its reserve capacity	- Chronic hepatitis - Cirrhosis - Liver cancer	- Minor: cirrhosis, hepatitis C, NASH - Moderate: **alcoholic hepatitis** - Severe: acute hepatitis	- Minor: infective hepatitis, **alcoholic hepatitis**, hepatitis, hepatocellular carcinoma - Moderate: extrahepatic obstruction, intrahepatic cholestasis - Severe: bone diseases	Moderate: infective hepatitis, prostate cancer High in **alcoholics**

Quiz

MCQs :

Q1: A patient presents with jaundice, abdominal pain, and nausea. Clinical laboratory results show increase in serum conjugated bilirubin, presence of urinary bilirubin but absence of urine urobilinogen. What is the most likely cause of the jaundice?

a) Decreased hepatic conjugation **b)** Decreased hepatic uptake
c) Decreased secretion of bile into the intestine **d)** Increased hemolysis

Q2: In post hepatic jaundice, ALT levels rise markedly.

a) True **b)** False

Q3: _____ is responsible for the yellow coloring in jaundice.

a) bilirubin **b)** urobilinogen **c)** urobilin **d)** stercobilin

Q4: Which of the following LFTs is more specific?

a) ALT **b)** Serum bilirubin **c)** alpha fetoprotein **d)** AST

Q5: Which of the following is produced in the bones?

a) GGT **b)** ALP **c)** Prothrombin **d)** AST

Q6: Which of the following markers indicate present liver function?

a) Serum albumin **b)** Prothrombin time **c)** GGT **d)** ALP

SAQs :

Q1: Name 3 markers related to cholestasis:

Q2: list the causes of pre hepatic , hepatic & post hepatic jaundice .

Q3: what do we observe when bilirubin serum is elevated ?

Q4: Name 3 markers observed in alcoholic liver disease:

★ **MCQs Answer key:**

1) C 2) B 3) A 4) A 5) B 6) B

★ **SAQs Answer key:**

1) Alkaline phosphatase (ALP) - γ-glutamyltransferase **(GGT) - bilirubin**
2) Slide 5
3) Gallstones , acute & chronic hepatitis
4) Serum globulin, ALP, ALT, GGT

Team members

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. "Opportunities don't happen. You create them."
★ -- Chris Grosser

We hear you