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SECTION C

Clinical and Applied Biochemistry

CHAPTER 24

Liver and Gastric Function Tests

ChapterataGlance

The learner will be able to answer questions on the following topics:

- Serum and urine bilirubin
- Tests based on synthetic function
- Enzymes indicating hepatocellular damage
- Gastric function and HCl secretion
- Gastric juice analysis
- Pancreatic function tests

Biochemical tests are of immense value in diagnosis and monitoring of liver diseases. These tests are usually referred to as "liver function tests" (LFT). LFTs are the most widely performed biochemical tests in the laboratory. Important liver functions are listed in Table 24.1. Often abnormal liver function will lead to jaundice (Fig. 24.1).

A long list of tests was formerly included under this group and were classified based on the major functions of liver. But nowadays, only clinically useful tests are being done. These liver function tests are broadly classified as

1. Tests to detect hepatic injury:
   a. To detect the disease, whether mild or severe; whether acute or chronic.
   b. To assess the nature of liver injury; hepatocellular or cholestasis.
2. Tests to assess hepatic function.

Problems in Interpretation

a. Normal LFT values need not indicate absence of liver disease, because liver has very large reserve capacity.
b. Asymptomatic people may have abnormal LFT results. So interpretation should be based on clinical picture.

FUNCTIONS OF LIVER

Synthetic Function

The plasma proteins albumin, alpha and beta globulins, clotting factors, carrier proteins, hormonal factors, growth factors, bile acids, cholesterol and phospholipids are the major biomolecules synthesized by the liver (Box 24.1).

Fig. 24.1: Jaundice

Carbohydrate Metabolism

Glucose may be metabolized to yield energy. If not, glucose can be stored as glycogen within the liver or it can be converted into more stable storage form as triglycerides. Homeostasis of blood glucose is described in Chapter 11.

Amino Acid Metabolism

Some of the proteins are produced only in the liver, examples are albumin, alpha and beta globulins and coagulation factors I, II, V, VII, IX and X (see Box 24.1). Several proteins of acute phase reactants are produced in the liver, e.g. C-reactive protein (infectious diseases).

Lipid Metabolism

Fatty acids will be catabolized to release acetyl CoA, and further to produce energy. Acetyl CoA is also used for fatty acid synthesis or cholesterol production. Dietary lipids are repackaged and secreted into the systemic circulation as lipoproteins. The protein parts of the lipoproteins, apoproteins are synthesized by the liver only. Lipoproteins are described in Chapter 14.

Bilirubin Metabolism

Heme is catabolized to bilirubin, which is transported as bilirubin-albumin complex. In the liver, bilirubin is conjugated with glurucronic acid, and finally excreted through bile (Chapter 22).

Box 24.1: Major functions of liver

1. Synthetic function
   a. Synthesis of plasma proteins (albumin, coagulation factors, many globulins)
   b. Synthesis of cholesterol
   c. Synthesis of triacyl glycerol
   d. Lipoprotein synthesis
2. Metabolic function
   a. Carbohydrates : Glycolysis; glycogen synthesis; glycogen breakdown; gluconeogenesis
   b. Ketogenesis; fatty acid synthesis and breakdown
   c. Protein catabolism
   d. Citric acid cycle, production of ATP
3. Detoxification and excretion
   a. Ammonia to urea
   b. Bilirubin (bile pigment)
   c. Cholesterol
   d. Drug metabolites
4. Homeostasis: Blood glucose regulation
5. Storage function : Vitamin A, D, K, B_{12}
6. Production of Bile salts; help in digestion

Detoxification Functions

Exogenous substances: Toxic substances entering from gut and parenteral route are mainly detoxified in the liver by different reactions. The cytochrome P450 enzyme system of hepatocyte is mainly concerned with drug metabolism (Chapter 36). **Endogenous substances:** Disposal of bilirubin is already discussed. Ammonia produced from amino acid catabolism is detoxified by the liver to form less toxic urea. The key urea cycle enzymes are located entirely in liver.

Excretory Functions

Substances detoxified by the liver are excreted through bile. About 3 liters of bile is produced daily and out of this 1 L is excreted and the rest is reabsorbed and circulated in the enterohepatic circulation. The bile contains bile salts, conjugated bilirubin, phospholipids and hormones. Major functions of the liver are summarized in Box 24.1.

CLINICAL MANIFESTATIONS OF LIVER DYSFUNCTION

Jaundice

Jaundice is the yellowish discoloration of sclera, skin and mucous membrane. It is characteristic of liver

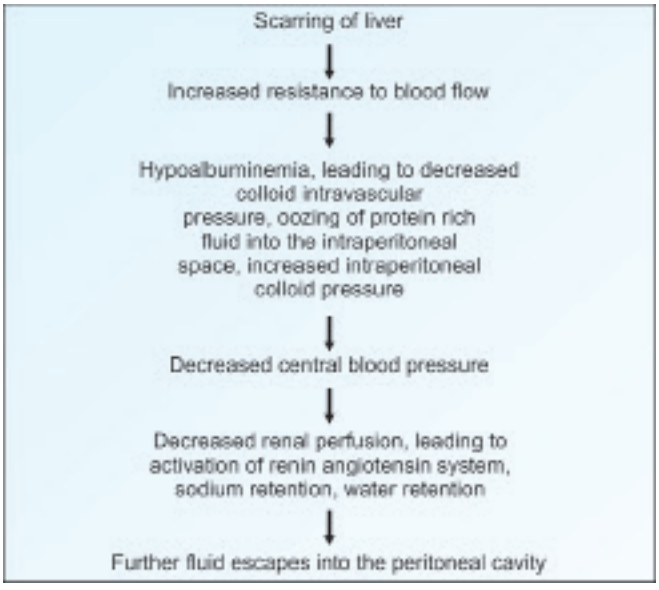

Fig. 24.2: Pathogenesis of ascites

disease but it will occur when rate of hemolysis is increased leading to elevation of serum bilirubin.

Portal Hypertension

The entire venous drainage of gastrointestinal tract, the spleen, the pancreas and the gallbladder constitutes portal circulation with a pressure of 5 mm of Hg. Any obstruction in the course of portal circulation will cause portal hypertension.

The major cause of portal hypertension is cirrhosis. Portosystemic shunting leads to deterioration of the metabolic functions of the liver. Failure of detoxification of ammonia by urea synthesis leads to hyperammonemia and hepatic encephalopathy. Decrease in albumin synthesis leads to hypoalbuminemia.

Ascites

It is due to effusion of serous fluid into the abdominal cavity. It is a common presenting feature of cirrhosis. Ascites may be due to different causes. If the ratio of serum albumin: ascitic fluid albumin is > 1.1, it is diagnostic of portal hypertension as the cause. Figure 24.2 explains the pathogenesis of ascites. Box 24.2 gives the indications of liver function tests. A detailed classification of the liver function tests (LFT) is shown in Table 24.1. Important liver function tests are described below:

Markers of Hepatic Dysfunction

Measurement of Bilirubin (Test of Excretory Function of Liver)

Bilirubin is the excretory product formed by the catabolism of heme. It is conjugated by the liver to form bilirubin diglucuronide and excreted through bile (see Chapter 22). Measurements of bilirubin is an important liver function test.

Box 24.2: Indications for liver function tests

1. Jaundice
2. Suspected liver metastasis
3. Alcoholic liver disease
4. Any undiagnosed chronic illness
5. Annual checkup of diabetic patients
6. Coagulation disorders
7. Therapy with statins to check hepatotoxicity

Normal serum bilirubin level varies from **0.2 to 0.8 mg/dL.** The unconjugated bilirubin (bilirubin-albumin complex) (free bilirubin) (indirect bilirubin) varies from 0.2–0.7 mg/dL and conjugated bilirubin (direct bilirubin) 0.1–0.4 mg/dL. A rise in serum bilirubin above 1 mg/dL is abnormal (latent jaundice); but jaundice appears only if the level goes above 2 mg/dL.

The bilirubin is estimated by **van den Bergh reaction,** where diazotized sulfanilic acid (sulfanilic

TABLE 24.1: Classification of liver function tests

A. Classification based on laboratory findings	
Group I (tests of hepatic excretory function)	
i.	Serum—bilirubin; total, conjugated, and unconjugated
ii.	Urine—bile pigments, bile salts and urobilinogen
Group II: Liver enzyme panel (see Chapter 6) (These are markers of liver injury and/or cholestasis)	
i.	Alanine amino transferase (ALT)
ii.	Aspartate amino transferase (AST)
iii.	Alkaline phosphatase (ALP)
iv.	Gamma glutamyl transferase (GGT)
Group III: Plasma proteins (see Chapter 26) (Tests for synthetic function of liver)	
i.	Total proteins
ii.	Serum albumin, globulins, A/G ratio
iii.	Prothrombin time
Group IV: Special tests	
i.	Ceruloplasmin (see Chapters 26 and 34)
ii.	Ferritin (see Chapter 34)
iii.	Alpha-1-antitrypsin (AAT)
iv.	Alpha fetoprotein (AFP) (see Chapter 48)
B. Classification based on clinical aspects	
Group I: Markers of Liver Dysfunction	
i.	Serum bilirubin, total, conjugated
ii.	Urine: Bile pigments, bile salts and UBG
iii.	Total protein, serum albumin and A/G ratio
iv.	Prothrombin time
v.	Blood ammonia, when indicated
Group II: Markers of hepatocellular injury	
i.	Alanine amino transferase (ALT)
ii.	Aspartate amino transferase (AST)
Group III: Markers of cholestasis	
i.	Alkaline phosphatase
ii.	Gamma glutamyl transferase

acid in HCl and sodium nitrite) reacts with bilirubin to form a purple colored complex, azobilirubin. When bilirubin is **conjugated**, the purple color is produced immediately on mixing with the reagent, the response is said to be van den Bergh **direct positive.** When the bilirubin is **unconjugated**, the color is obtained only when alcohol is added, and this response is known as **indirect positive**. If both conjugated and unconjugated bilirubin are present in increased amounts, a purple color is pro- duced immediately and the color is intensified on adding alcohol. Then the reaction is called **biphasic**.

In **Hemolytic** jaundice, unconjugated bilirubin is increased. Hence van den Bergh test is indirect positive. In **obstructive** jaundice, conjugated bilirubin is elevated, and van den Bergh test is direct positive. In **hepatocellular** jaundice, a biphasic reaction is observed, because both conjugated and unconjugated bilirubins are increased (see Chapter 22).

Urinary Bilirubin

In all cases of jaundice, urine should be examined for the presence of bile pigments (bilirubin), bile salts and urobilinogen. Only conjugated bilirubin is soluble in water and is excreted in urine. Hence in prehepatic jaundice, when the unconjugated bilirubin is increased in blood, it does not appear in urine. But in obstructive jaundice, conjugation of bilirubin is taking place, which cannot be excreted through the normal passage, and so it is regurgitated back into bloodstream; this is then excreted through urine. So in obstructive jaundice, urine contains bilirubin.

Urinary Urobilinogen

In cases of obstruction, bile is not reaching the intestine and so urobilinogen may be decreased or absent in urine. In hepatocellular jaundice, urobilinogen is initially elevated, then decreases or disappears when the obstructive stage sets in and reappears when obstruction is cleared. Urobilinogen is absent in urine, when there is obstruc- tion to bile flow. The **first indication of recovery is the reappearance of urobilinogen** in urine. In hemolytic anemias, urobilinogen is increased. Bilirubin is detected by Fouchet's test and urobilinogen by Ehrlich's test. The findings in urine in different types of jaundice are shown in Table 24.2. Table 24.3 shows the classification and causes for jaundice. Table 24.4 gives the tests to distinguish different types of jaundice. Bilirubin synthesis, excretion and jaundice are described in detail in Chapter 22.

Urine Bile Salts

Normally bile salts (sodium salts of taurocholic acid and glycocholic acid) are present in the bile; but are not seen in urine. Bile salts in urine are detected by **Hay's test**. Positive Hay's test indicates the obstruction in the biliary passages causing regurgitation of bile salts into the systemic circulation leading to its excretion in urine. Obstruction can occur in obstructive jaundice and also in hepatic jaundice due to obstruction of micro biliary channels caused by inflammation.

Causes of Jaundice

Causes of jaundice are enumerated in Boxes 24.3 and 24.4. The most common cause for hepatocellular jaundice is infection with hepatitis viruses (viral

TABLE 24.2: Urinary findings in jaundice

Type of jaundice	*Bile pigment*	*Bile salt*	*Urobilinogen*
Pre-hepatic (hemolytic)	Nil	Nil	++
Hepatocellular	++	+	Normal
Post-hepatic (obstructive)	+++	++	Nil

TABLE 24.3: Classification of jaundice

Type of bilirubin	*Class of jaundice*	*Causes*
Unconjugated	Prehepatic or hemolytic	Abnormal red cells; antibodies; drugs and toxins; thalassemia; hemoglobinopathies. Gilbert's syndrome; Crigler-Najjar syndrome
Unconjugated and conjugated	Hepatic or hepatocellular	Viral hepatitis; toxic hepatitis; intrahepatic cholestasis
Conjugated or obstructive	Post-hepatic	Extrahepatic cholestasis; gallstones; tumors of bile duct; carcinoma of pancreas; lymph node enlargement in porta hepatis

hepatitis). It may be due to **hepatitis A virus** (HAV), which is transmitted by the intake of contaminated food and water. Type A disease is usually self-limiting.

Infection by **hepatitis B virus** (HBV) is transmitted mainly through parenteral contamination by infected blood or blood products. The virus is highly contagious and can be destroyed only by boiling for 20 minutes. It is a DNA virus, which destroys the hepatic cells. The **surface antigen** (HBs) is seen in the circulation of patients. For his contributions in hepatitis prevention, Baruch Blumberg was awarded Nobel prize in 1976. About 5% of world populations are carriers of HBV. In about 2–5 % cases, the disease passes on to a chronic carrier state. About 1% of cases progress to chronic cirrhosis and eventual hepatic failure.

In a small fraction of such cases, development of hepatocellular carcinoma is also noticed. Thus HBV is an **oncogenic virus**. Medical personnel, including medical students, doctors, nurses and technicians are advised to take Hepatitis B vaccination. Hepatitis viruses type A, B, C, D, E and G are identified. Box 24.5 gives the serology to define the type of viral hepatitis.

Tests Based on Synthetic Function of Liver

Serum Albumin Level

Almost all the plasma proteins except immunoglobulins are synthesized by the liver. Serum **albumin** (see Chapter 26) is quantitatively the most important protein synthesized by the liver, and reflects the extent of functioning liver cell mass. Since albumin has a fairly long half-life of 20 days, in all chronic diseases of the liver, the albumin level is decreased (See Chapter 26).

Normal albumin level in blood is 3.5 to 5 g/dL; and globulin level is 2.5 to 3.5 g/dL. The turnover rates of haptoglobin and transferrin are lesser than albumin; hence they are useful to identify recent changes in liver functions.

van den Bergh
1869–1943

Baruch Blumberg
NP 1976
1925–2011

Barry J Marshall
NP 2005
b. 1951

Robin Warren
NP 2005
b. 1937

TABLE 24.4: Tests useful to distinguish different types of jaundice

Specimen	*Test*	*Pre-hepatic or hemolytic or retention jaundice*	*Hepatocellular jaundice*	*Post-hepatic or obstructive or regurgitation jaundice*
Blood	Unconjugated bilirubin (van den Bergh indirect test)	++	++	Normal
	Conjugated bilirubin (van den Bergh direct test)	Normal	Excretion is rate-limiting. It is the first impaired activity. In early phase, it is increased	++
	Alkaline phosphatase (40–125 U/L)	Normal	2–3 times increased	10–12 times
Urine	Bile salt (Hay's test)	Absent	Absent	Present
	Conjugated bilirubin (Fouchet's)	Absent	Present	Present
	Urobilinogens (Ehrlich test)	+++	Increased in early cholestatic phase; Absent later decreased as production is low. Earliest manifestation of recovery is presence of bilinogen in urine	Absent
Feces	Urobilins	++	Normal or decreased	Clay colored

Serum Globulins

Immunoglobulins are produced by B lymphocytes. But alpha and beta globulins are synthesized mainly by hepatocytes. Gamma globulins in the serum are increased in chronic liver diseases (chronic active hepatitis, cirrhosis). Further details of immunoglobulins are given in Chapter 46.

Prothrombin Time (PT)

Since prothrombin is synthesized by the liver, it is a useful indicator of liver function. The half life of prothrombin is 6 hours only; therefore PT indicates the present function of the liver. PT is prolonged only when liver loses more than 80% of its reserve capacity. Vitamin K deficiency is also a cause for prolonged prothrombin time. In case of liver disease, the PT remains prolonged even after parenteral administration of vitamin K.

Box 24.3: Causes of cholestatic liver disease

1. Extrahepatic cholestasis
   - Cholelithiasis (stone in gallbladder)
   - Carcinoma head of pancreas
   - Portal lymphadenopathy
   - Chronic pancreatitis
   - Biliary stricture
   - Parasites (liver flukes) (rare in India)
2. Intrahepatic cholestasis
   - Alcoholic cirrhosis
   - Primary biliary cirrhosis
   - Non-alcoholic steatohepatitis (NASH)
   - Viral hepatitis (cholestatic phase)
   - Protoporphyria
   - Dubin-Johnson syndrome
3. Drugs
   - Androgens, Chlorpromazine
   - Chlorpropamide, Nitrofurantoin
   - Erythromycin, Phenytoin
   - Cyclosporine, Captopril

Box 24.4: Causes of hepatocellular damage

1. *Viruses:* HAV, HBV, HCV, Herpes, Adenovirus
2. Alcohol
3. *Toxins:* Carbon tetracholoride, Chloroform, Mushroom, Aflatoxin, Arsenic
4. *Immunological:* Autoimmune hepatitis, NASH
5. *General diseases:* Wilson's disease, Hemochromatosis, AAT deficiency, Porphyrias, Sarcoidosis, Amyloidosis
6. *Neoplasm:* Hepatocellular carcinoma, Metastatic liver disease, Lymphoma
7. *Bacterial infections:* TB, Leptospirosis, Brucella, Abscesses
8. *Parasites:* Helminths, Amebiasis, Plasmodia, Leishmania
9. *Drugs:* Salicylate, Tetracyclines, Methotrexate, Isoniazid, Rifampicin, Halothane, Methyldopa, Valproate

Alpha fetoprotein (AFP)

It is a normal component of fetal blood. It disappears after birth within a few weeks. It is a **tumor marker** (Chapter 48). Mild elevation is suggestive of chronic hepatitis or cirrhosis; drastic increase is seen in hepatocellular carcinoma, germ cell tumors and teratoma of ovary. Elevated AFP in the maternal serum is seen in cases of fetal open **neural tube defects**.

Other important serum proteins, synthesised by the liver, are ceruloplasmin, transthyretin, alpha-1-antitrypsin and haptoglobin. These are described in Chapter 26.

Serum Electrophoresis

Abnormal electrophoretic patterns are shown in Figure 26.1. **Pre-albumin** is reduced in acute hepatitis. **Albumin** is decreased in cirrhosis. **Alpha-1 globulins** band is decreased in hepatocellular disease almost parallel to albumin. It is increased in febrile illnesses and malignancies. **Alpha-2 globulins and beta globulins**, when increased suggest biliary obstruction. **Gamma globulins** are increased in cirrhosis. The rise in gamma globulin will have wide base, suggestive of polyclonal gammopathy.

Tests Based on Serum Enzymes (Liver Enzyme Panel)

The enzymes used in the assessment of hepatobiliary disease may be divided into two groups: (a) Those indicating hepatocellular damage and; (b) Those indicating cholestasis (obstruction).

Box 24.5: Serology to define viral hepatitis type

Hepatitis A	Anti-HAV IgM
Hepatitis B acute	HBsAg, anti-HBc IgM
Hepatitis B chronic	HBsAg, HBeAg, HBV DNA
Hepatitis C	Anti-HCV and HCV RNA
Hepatitis D (delta)	HBsAg and anti-HDV
Hepatitis E	Anti-HEV

Enzymes Indicating Hepatocellular Damage

Liver enzyme panel is described in detail in Chapter 6. Normal serum ALT (alanine amino transferase) is 10–35 IU/L. The levels of **amino transferases** (ALT and AST) in serum are elevated in all liver diseases (Box 24.7). **Very high levels** (more than 1000 units) are seen in acute hepatitis (viral and toxic). The degree of elevation may reflect the extent of hepatocellular necrosis. In most cases the lowering of the level of transaminases indicates recovery, but a sudden fall from a very high level may indicate poor prognosis. Elevation of ALT is more in cases of hepatic disease compared to AST. A ratio of AST/ALT more than two is quite suggestive of alcoholic liver disease.

Moderate elevation of amino transferases often between 100–300 U/L is seen in **alcoholic** hepatitis-and non- alcoholic chronic hepatitis (Box 24.7). **Minor elevation** less than 100U/L is seen in chronic viral hepatitis, fatty liver and in non- alcoholic steatohepatitis (**NASH**). A normal value need not rule out minor liver diseases.

Markers of Obstructive Liver Disease

Alkaline Phosphatase (ALP)

Very high levels of alkaline phosphatase (ALP) are noticed in patients with cholestasis or hepatic carci noma. Bile duct obstruction induces the synthesis of the enzyme by biliary tract epithelial cells (see Chapter 6). In **parenchymal diseases** of the liver, mild elevation of ALP is noticed. But in hepatitis, inflammatory edema produces an obstructive phase, during which ALP level is elevated. (Table 24.4). Very high levels of ALP (10–12 times of upper limit) may be noticed in extrahepatic **obstruction** (obstructive jaundice) caused by gallstones or by pressure on bile duct by carcinoma of head of pancreas.

Intrahepatic cholestasis may be due to virus (infective hepatitis) or by drugs (chlorpromazine). ALP is produced by epithelial cells of biliary canaliculi and obstruction of bile with consequent irritation of epithelial cells leads to secretion of ALP into serum. Drastically high levels of ALP (10–25 times of upper limit) are seen in **bone diseases** where osteoblastic activity is enhanced. For example, Paget's disease (osteitis deformans), rickets, osteomalacia, osteoblastoma, metastatic carcinoma of bone and hyperparathyroidism.

Gamma Glutamyl Transferase (GGT)

GGT is clinically important because of its sensitivity to detect **alcohol abuse**. GGT level in alcoholic liver disease roughly parallels the alcohol intake (see Chapter 6). Elevated levels of GGT are observed in chronic alcoholism. In liver diseases, GGT elevation parallels that of ALP and is very sensitive of biliary tract disease.

Tests for Metabolic Capacity of Liver

Blood Ammonia

It is an index of urea synthesis by liver. It is a useful test in **hepatic encephalopathy**. It is produced by action of intestinal bacteria. The ammonia is later converted to urea by the liver, but this activity is considerably decreased in hepatic cell damage. In neonates suspected to have urea cycle disorders (and in organic acidurias), ammonia estimation is indicated.

Precautions: Fasting plasma/serum is used for ammonia estimation. Stringent precautions are to be maintained. Vacutainers must be used and the blood withdrawn until it is full. Partial filling allows entry of air. Sample should be immediately placed in ice and carry out the assay as soon as possible.

The clinical features of acute liver failure are shown in Box 24.6.

Immunological Tests in Liver Disease

IgG level is increased in chronic hepatitis, alcoholic and autoimmune hepatitis.It shows a slow and sustained increase in viral hepatitis. **IgM** shows marked increase in primary biliary cirrhosis and moderate increase in viral hepatitis and cirrhosis. **IgA** is increased in alcoholic cirrhosis and primary biliary cirrhosis (Table 24.5).

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Selection of Tests

Liver function tests are the most common group of biochemical tests done to diagnose and monitor the course of liver disease. The increased incidence of infectious diseases like viral hepatitis and leptospirosis

requires these tests to be done in all patients with unexplained illness.

Several different tests are to be done for overall assessment of the liver function. Table 24.6 gives the different tests and the alterations in different types of liver diseases.

Most commonly employed liver function tests in clinical practice are serum bilirubin, albumin, ALP, ALT, AST and GGT. Cholesterol level in blood is also increased in obstructive jaundice due to defective excretion through bile. In general, ALT and ALP distinguishes the pattern of liver disease. Albumin determines the chronicity and prothrombin time determines the severity of liver dysfunction (Box 24.8).

Gastric Function Tests

The gastric mucosa has different types of cells: (a) The mucous secreting surface epithelial cells, (b) The oxyntic or parietal cells which secrete acid, and (c) The chief cells or peptic cells that secrete enzymes.

Box 24.6: Clinical features of acute liver failure

Liver
Loss of metabolic function
Decreased gluconeogenesis leading to hypoglycemia
Decreased lactate clearance leading to lactic acidosis
Decreased ammonia clearance leading to hyperammonemia
Decreased synthetic capacity leading to coagulopathy
Portal hypertension

Lungs
Adult respiratory distress syndrome

Adrenal gland
Inadequate glucocorticoid production contributing to hypotension

Bone marrow
Frequent suppression, especially in viral diseases

Circulating leukocytes
Impaired function contributing to sepsis

Brain
Hepatic encephalopathy
Cerebral edema
Intracranial hypertension

Heart
Subclinical myocardial injury

Kidney
Frequent dysfunction or failure

Mechanism of HCl Secretion

The daily volume of gastric secretion is around 2000 mL. The HCl secreted by the parietal cells is of high concentration (0.15 M) with a pH as low as 0.8. The parietal cells transport protons against a concentration gradient. It is an energy requiring process. The K^+ activated ATPase is necessary for the produc- tion of HCl (Fig. 24.3). The H^+ ions are generated within the cell by ionization of carbonic acid. The carbonic anhydrase is active in the parietal cells. One molecule of ATP is hydrolyzed for every molecule of H^+ secreted. The hydrolysis of ATP is coupled with an exchange of K^+ for H^+. The hydrogen ions are then secreted into gastric lumen.

Side by side with the H^+ to K^+ exchange, bicarbonate to chloride exchange is also taking place (Fig. 24. 3). When the bicarbonate level within the cell increases (formed from H_2CO_3), it is reabsorbed into blood stream, in exchange for Cl^-. The chloride is then secreted into the lumen to form HCl. This would account for the **alkaline tide** of plasma and urine, following hydrochloric acid secretion, immediately after meals.

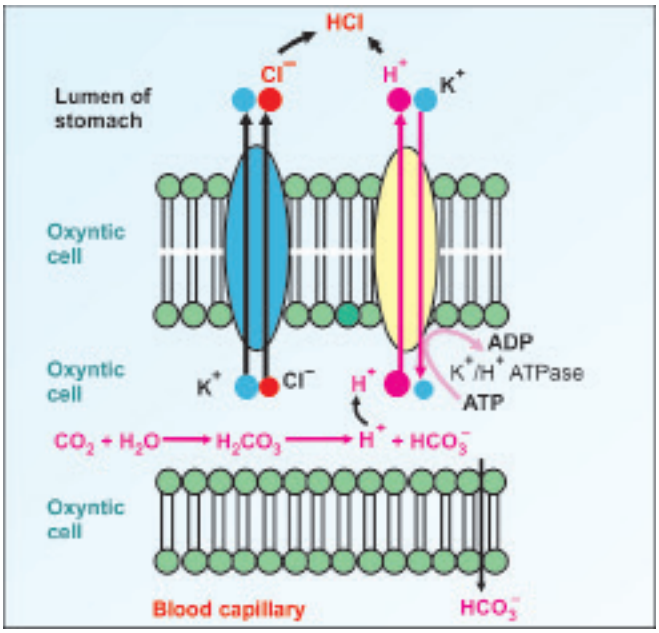

Fig. 24.3: Hydrochloric acid secretion

Regulation of Acid Secretion

i. **Gastrin**, the gastrointestinal peptide hormone secreted by G cells, stimulates secretion of HCl. The secretion of gastrin is cut off by acidic pH by a feedback regulatory control.
ii. The most potent stimulus for acid secretion is **histamine,** which acts through specific H_2 receptors on the gastric mucosa.

Assessment of Gastric Function

In **Fractional test meal** or FTM, the fasting stomach contents are aspirated and the secretion is stimulated by giving test meals. Different samples are collected and the acidity (free and total) of each sample is measured. The FTM is not done nowadays; but the modified version, though rare, is still in use. It is described below.

Box 24.8: Liver regeneration

Prometheus was punished for stealing fire from the Gods. As punishment he was chained to rocks and his liver was pecked by vultures everyday. However, he survived. How?

About 90% of liver can be removed and still the remaining liver cells re-enter cell cycle and divide replacing the lost cells within weeks. The story tells us that this ability of liver cells to regenerate was known even from ancient days.

TABLE 24.5: LFT in autoimmune hepatitis

	Cases not in active state	*Active or advanced*
Serum bilirubin	Normal	3 – 10 mg%
Albumin	Normal	Decreased
Globulin	< 2.5 g %	> 2.5 g%)
ALP	Normal	Increased
Transaminases	<100 U/L	100 – 1000 U/L
PT	Prolonged	Prolonged
Autoantibodies anti LKM1	ANA (Anti nuclear antibody)	ANA, smooth muscle ab

Box 24.7: Clinical significance of AST/ALT ratio

Normal AST: ALT ratio is 0.8. A ratio >2 is seen in
- Alcoholic hepatitis
- Hepatitis with cirrhosis
- Non-alcoholic steatohepatitis (NASH)
- Liver metastases
- Myocardial infarction
- Erythromycin treatment

A low ratio (ALT is higher) is seen in
- Acute hepatocellular injury
- Toxic exposure
- Extrahepatic obstruction (cholestasis)

TABLE 24.6: Overview of liver function tests

Parameter	*Remarks*
Serum albumin	In chronic liver disease
Serum globulins	Increase in chronic hepatitis
PT	Prolonged in liver disease
PT + vitamin K	Prolonged in hepatocellular If PT normal, cholestasis
Alpha fetoprotein	Increase in carcinoma
Ceruloplasmin	Decrease in Wilson's disease, Menke's disease
Transthyretin	To assess nutritional status
Alpha-1antitrypsin	Decrease in neonatal cholestasis, progressive juvenile cirrhosis, micronodular cirrhosis
Haptoglobin Transferrin	Severe hepatocellular disease cirrhosis.
Lipoprotein X	Increase in cholestasis
Galactose	Half-life >12 minutes in tolerance test cirrhosis, infective hepatitis
Amino acids	Increased aromatic amino acids + branched chain aminoacids in hepatic coma; both increased in cirrhosis
Serum bilirubin	See Table 24.4.
Urine bilirubin	See Table 24.4
Urine urobilinogen	See Table 24.4
Plasma bile acids	Post-prandial rise in hepatic dysfunction; increased fasting level in portosystemic shunting
Urine bile salts	Positive in post-hepatic jaundice and hepatic jaundice
Ammonia	Increase in cirrhosis, portocaval anastamosis
Transaminases	
Viral hepatitis	ALT and AST increased
Chronic active hepatitis	N or slight increase
Cholestasis	Slight increase
Alcoholic hepatitis	ALT/AST ratio reversed
ALP	Increase in cholestasis
GGT	Increase in cholestasis

Pentagastrin Stimulation Test

In the fasting condition, the gastric juice is aspirated through a Ryle's tube (Residual juice). The gastric juice secreted for the next 1 hour is collected as a single sample (**Basal secretion**). The gastric secretion is now stimulated by giving pentagastrin. It is a synthetic peptide having the biologically active sequence of gastrin. The gastric secretion is collected every 15 minutes for the next 1 hour.

Basal acid output (BAO) is the acid output in millimol per hour, in the basal secretion (in the absence of all intentional and avoidable stimulation).

Maximal acid output (MAO) is the acid output in millimol per hour, given by the sum of the acid output of the four 15-minute samples after the stimulation.

Peak acid output (PAO) is the acid output in millimol per hour, given by the sum of the acid output of the 2 consecutive 15-minute samples having the highest acid content. Normal values are given in Table 24.7.

Interpretations of Gastric Juice Analysis

Zollinger-Ellison syndrome. This condition results from a gastrin secreting tumor (gastrinoma of the pancreas). There is no feedback regulation of gastrin secretion. There is very high level of gastric acid output along with elevated serum gastrin levels. In this condition, BAO is >15 mmol/h (may be as high as 150 mmol/h) and BAO/PAO ratio is 0.6 or higher.

In chronic duodenal ulcer, BAO, MAO and PAO are significantly elevated. BAO may vary from 4–6 mmol/h and a BAO/PAO ratio of more than 0.3 indicates increased basal secretory drive. Causes for hyperacidity and hypoacidity are shown in Box 24.9.

Gastric ulcers are perpetuated by the infection of ***Helicobacter pylori***. Marshall and Warren were awarded Nobel Prize in 2005 for their discovery of the bacterium *H. pylori* and its role in acid peptic disease. The bacteria produce ammonia, with the help of bacterial urease. So, the organism can escape the attack of acidic gastric juice. *H. pylori* infection is identified by presence of urease enzyme in gastric biopsies and detecting *H.pylori* antibodies in serum.

Pancreatic Function Tests

The exocrine pancreas secretes about 1000–2500 mL of juice in 24 hours. The fluid is alkaline and contains bicarbonate and enzymes. This secretion is under the control of the hormones, **Secretin** and **Cholecystokinin**. Secretin is produced under the stimulation of gastric HCl. Secretin produces a secretion with high bicarbonate content. Gastrin stimulates production of cholecystokinin (CCK), which in turn produces pancreatic secretion rich in enzymes. The major enzymes present in pancreatic juice are amylase, lipase and proteolytic enzymes (trypsin, chymotrypsin, carboxypeptidase, elastase) as their zymogens (see Chapter 17).

Assessment of Pancreatic Function

Measurement of pancreatic enzymes: Amylase or alpha-1,4-glucosidase is the major enzyme which digests starch. Normal amylase level in serum is 50–120 units. The level rises within 5 hours of the onset of **acute pancreatitis** and the level reaches a peak within 12 hours. But the level need not parallel the severity of the disease. Within 2–4 days of the attack, the level returns to normal.

$$CR = \frac{\text{Urine amylase level}}{\text{Serum amylase level}} \times \frac{Scr}{Ucr} \times 100$$

Amylase level in blood is mildly increased in cases of cholecystitis. No significant change or only mild elevation is noticed in chronic pancreatitis.

Serum lipase is the major lipolytic enzyme which hydrolyzes glycerol esters of long chain fatty acids. The level in blood is highly elevated in **acute pancreatitis** and this persists for 7 – 14 days. Thus lipase remains elevated longer than amylase. Moreover, lipase is not increased in salivary diseases. Therefore, lipase estimation has advantage over amylase.

Lundh test: The test meal is composed of milk powder, vegetable oil and glucose to make 6% fat, 5% protein and 15% carbohydrate. After aspirating the duodenal contents, 500 mL of fluid meal is given. Then duodenal secretions are collected at 30 minutes intervals for 2 hours. The tryptic activity of duodenal aspirates are measured. In chronic pancreatitis, the tryptic activity is decreased, but not in carcinoma of pancreas.

STUDIES ON MALABSORPTION

Malabsorption may result from defective digestion or faulty absorption or from both. Reduction of absorptive surface may result from i) Celiac disease; ii) Gluten sensitive enteropathy; iii) Tropical sprue; iv) Ideopathic steatorrhea; v) Extensive surgical removal of ileum; vi) Crohn's disease or vii) Whipple's disease. Pancreatic disease can lead to defective digestion. The following tests are useful to assess the malabsorption states.

Fat balance studies: The estimation of fat in stool is done. When feces contains split fatty acids, it points to a normal pancreatic function, but defective absorption. On the other hand, if the fat excreted is neutral fat, it is due to defective digestion, and is more in favor of pancreatic disease.

Clinical Case Study 24.1

A 45-year-old male with history of cirrhosis of the liver is brought to the emergency center by family members for acute mental derangements, disorientation alterations in personality and confusion over the last few days. Patient is vomiting blood. On examination, he is disoriented with evidence of icteric sclera. His abdomen is distended with a fluid wave appreciated. His urine drug screen and ethyl alcohol (EtOH) screen are both negative. A blood ammonia level was elevated, and all other tests have been normal.

What is the most likely cause of the patient's symptoms? What was the likely precipitating factor of the patient's symptoms? What is the cause for fluid in abdomen?

Box 24.9: Causes for hyper and hypoacidity

Hyperacidity is seen in

i. Duodenal ulcer
ii. Gastric cell hyperplasia
iii. Carcinoid tumors
iv. Zollinger-Ellison syndrome
v. MEN (multiple endocrine neoplasia)
vi. Excessive histamine production as in systemic mastocytosis and basophilic leukemia.

Hypoacidity is seen in

i. Gastritis
ii. Gastric carcinoma
iii. Partial gastrectomy
iv. Pernicious anemia
v. Chronic iron deficiency anemia.

TABLE 24.7: Normal hydrochloric acid secretion

	Acid output in mmol/hour			
	Men		*Women*	
	Lower limit	*Upper limit*	*Lower limit*	*Upper limit*
Basal acid output	–	10	–	5.5
Maximal acid output	7	45	5	30
Peak acid output	12	60	8	40

Clinical Case Study 24.2

A 45-year-old female presents to the clinic with midepigastric pain and nausea/vomiting after eating "greasy meals". The symptoms gradually disappear, and return after some days. She denies any hematemesis. She had elevated cholesterol levels. On examination, she is afebrile with normal vital signs. Her physical examination is completely normal with no evidence of abdominal pain. An abdominal ultrasound is performed and revealed a few gallstones in the gallbladder. What factors would you need to consider to assess the need for cholecystectomy? What are gallstones made of? Can gallstones be seen on abdominal X-ray?

Clinical Case Study 24.3

A 26-year-old female at 35 weeks gestation presents to the clinic with complaints of generalized itching (pruritis). She denies any change in clothing detergent, soaps, or perfumes. She denies nausea and vomiting. On physical examination, there are no rashes apparent on her skin. Blood test reveals slightly elevated serum transaminase and bilirubin levels. What is the patient's likely diagnosis? What are treatment options? What is the cause of the patient's generalized itching?

Clinical Case Study 24.1 Answer

The likely cause is Cirrhosis.

Patient presents with cirrhosis, most probably, secondary to hepatitis virus infection, with acute mental status change coinciding with recent onset of hematemesis. Patient has an elevated serum ammonia level and otherwise negative workup. Hepatic encephalopathy

(disorientation, etc.) is secondary to elevated ammonia levels. The precipitating factor is increased nitrogen load from upper gastrointestinal bleeding.

Cirrhosis is a chronic condition of the liver with diffuse parenchymal injury and regeneration leading to distortion of the liver architecture and increased resistance of blood flow through the liver. The patient usually manifests malaise, lethargy, palmar erythema, ascites, jaundice, and hepatic encephalopathy in the late stages. Toxins accumulating in the bloodstream affect the patient's mental status. The most common etiologies of cirrhosis are toxins such as alcohol, viral infections such as hepatitis B or C infection, or metabolic diseases in children (Wilson disease, hemochromatosis, or alpha-1-antitrypsin deficiency). As liver functions are reduced, albumin synthesis is lowered, which leads to ascites (fluid in abdomen).

Clinical Case Study 24.2 Answer

Gallstones

Surgical removal of gallbladder (cholecystectomy) is done when there is frequent and severe attacks. **Components of gallstones are c**holesterol, calcium bilirubinate, and bile salts.

Mixed stones are much easier to see on plain film secondary to calcifications, comprising approximately 10 percent of gallstones. This individual fits the "classic" patient with gallbladder disease—female, middle-aged, overweight. The gallbladder stores bile salts produced by the liver. The gallbladder is stimulated to contract when food enters the small intestine; the bile salts then travel through the bile duct to the duodenum. The bile salts act to emulsify fats, helping with the digestion of fat. Gallstones form when the solutes in the gallbladder precipitate. Cholesterol stones are usually yellow-green in appearance and account for approximately 80% of gallstones. Stones made of bilirubin appear dark in color. Patients may have pain from the gallstones, usually after a fatty meal. The pain is typically epigastric or right upper quadrant and perhaps radiating to the right shoulder. If the gallbladder becomes inflamed or infected, cholecystitis can result. The stones can also travel through the bile duct and obstruct biliary flow leading to jaundice, or irritate the pancreas and cause pancreatitis.

Clinical Case Study 24.3 Answer

Cholestasis of pregnancy

Treatment options: Oral antihistamines

Etiology: Cholestasis of pregnancy is a condition in which the normal flow of bile from the gallbladder is impeded, leading to accumulation of bile salts in the body. Generalized itching and, possibly, jaundice may result. It is speculated that the hormones such as estrogen and progesterone, which are elevated in pregnancy, cause a slowing of the gallbladder function, leading to this disorder. Uncomplicated cholestasis is usually diagnosed clinically by generalized itching in a pregnant woman, usually in the third trimester without a rash. Elevated serum bile salts, bilirubin and transaminase may also be seen. The usual treatment includes antihistamine medications for the itching. Liver function and may reduce the serum bile acid concentration. More severe cases may require bile salt binders such as cholestyramine or corticosteroids.

LEARNING POINTS, CHAPTER 24

1. Bilirubin is estimated by van den Bergh reaction. Normal serum does not give a positive van den Bergh reaction.
2. When bilirubin is conjugated, the purple color is produced immediately on mixing with the reagent, the response is said to be van den Bergh direct positive. When the bilirubin is unconjugated, the color is obtained only when alcohol is added, and this response is known as indirect positive.
3. The most common cause for hepatocellular jaundice is the infection with hepatitis viruses (viral hepatitis).
4. Elevated levels of Gamma Glutamyl Transferase (GGT) are observed in chronic alcoholism, pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease and in diabetes mellitus.
5. High levels of alkaline phosphatase (ALP) are noticed in patients with cholestasis or hepatic carcinoma.

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