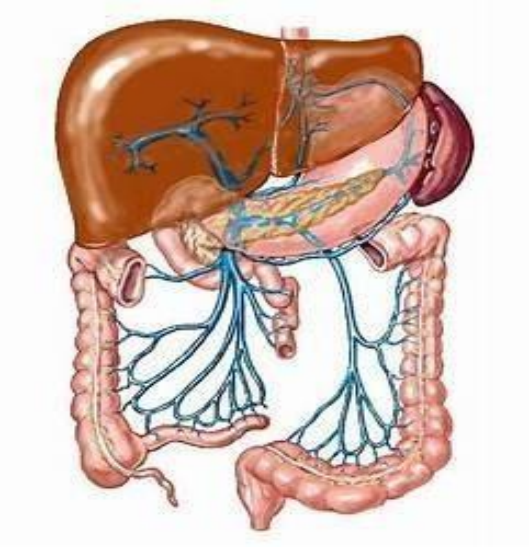
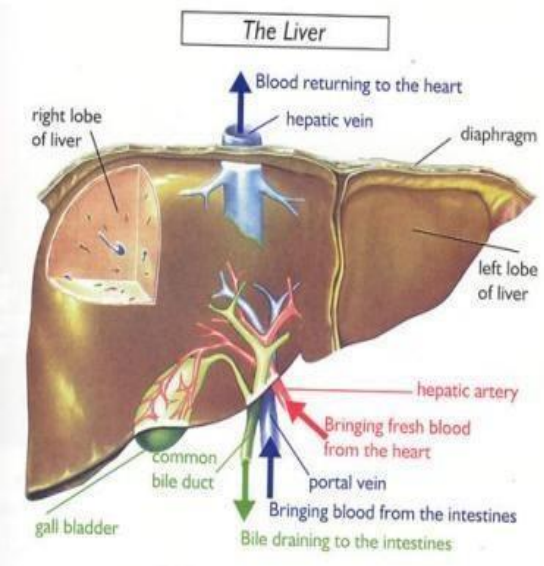
Liver Functions and Liver Functions Tests
Lectures 11

Liver:

Two main liver lobes are each made up of thousands of lobules. The liver regulates, synthesizes, stores and secretes many important proteins and nutrients, and purifies, transforms and clears toxic or unnecessary compounds from the blood.





Liver

Two main liver lobes are each made up of thousands of lobules; lobules connect to small ducts that connect to larger ducts, forming the hepatic duct. The hepatic duct transports bile, produced by the hepatocytes, to the gallbladder and duodenum. Blood leaves the stomach and intestines, gastric and spleen, passing through the liver (hepatic portal vein), while oxygenated blood is supplied through the hepatic artery.

The liver regulates, synthesizes, stores and secretes many important proteins and nutrients, and purifies, transforms and clears toxic or unnecessary compounds from the blood. Hepatocytes are optimized for function through their contact with sinusoids (leading to and from blood vessels) and bile ducts. A special feature of the liver is its ability to regenerate, maintaining function even in the face of moderate damage.

Bilirubin

In adults some 250–400 mg of bilirubin is produced daily; 70–80% is derived from degradation of the haem moiety of haemoglobin, 20–25% is derived from the hepatic turnover of haem proteins, such as myoglobin, cytochromesand catalase.

Bilirubin is a potentially toxic catabolic product of haem metabolism. It is poorly soluble in water at physiologic pH, and conversion to a water-soluble form is essential for elimination by the liver and kidney. Within the hepatocyte, theenzyme glucuronyl transferase UGT-1 covalently attaches one or two molecules of glucuronic acid to bilirubin, generating either bilirubin mono- or di-glucuronide. These glucuronic acid-attached species of bilirubin are termed "Conjugated Bilirubin" and are now water soluble.

Conjugated Bilirubin cannot be transported past the GI mucosa and so travels down the GI Tract. However, the normal GI bacterial flora convert the vast majority of conjugated bilirubin to colorless "Urobilinogen" and a small amount to brown-colored "Urobilin". About 90% of urobilinogen is excreted along with the feces; however, about 10% is resorbed by the GI Mucosa and enters the blood stream where it is once again recaptured by hepatocytes and re-excreted in the bile. The majority of urobilin is also excreted in the feces, giving it the characteristic brown color after converted to stercobilin; however, a small minority is resorbed by the GI mucosa and is ultimately excreted by the kidneys, giving urine its yellowish hue.

Jaundice

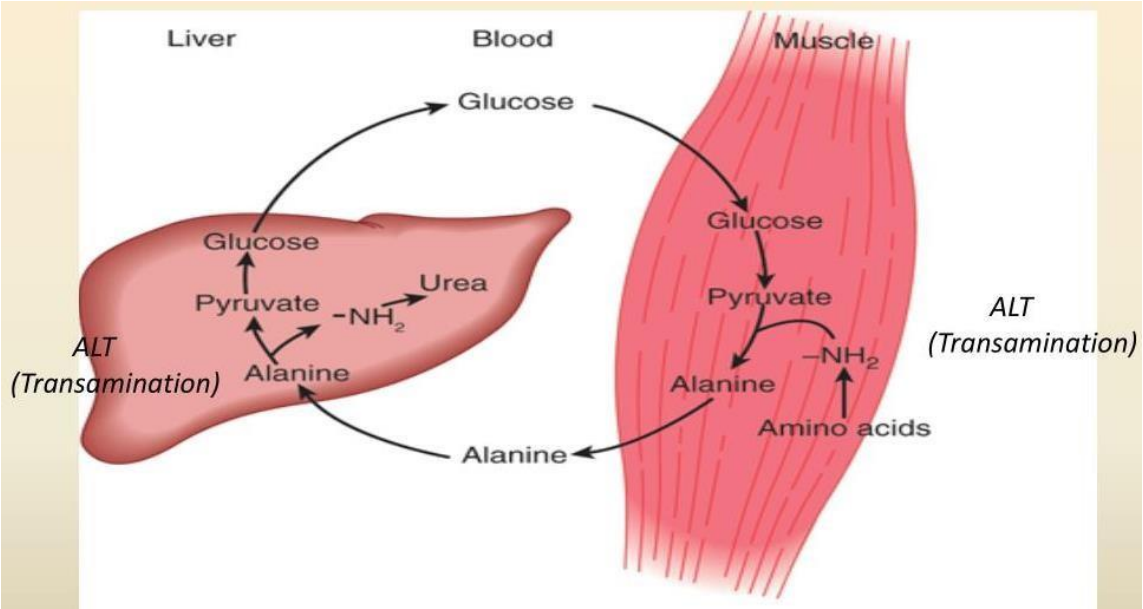
Jaundice is a clinical term referring to yellowing of body tissues due to deposition of bilirubin. Because bilirubin has a high affinity for the sclera of the eye, the most sensitive indicator of Jaundice is yellowing of the sclera, termed scleral icterus, which occurs when plasma bilirubin levels are greater than 3.0mg/dl.

Bilirubin type	Bilirubin level
Total bilirubin	0.3–1.0 mg/dl or 5.1–17.0 mmol/l
Direct bilirubin	0.1–0.3 mg/dl or 1.7–5.1 mmol/l
Indirect bilirubin (total bilirubin level minus direct bilirubin level)	0.2–0.8 mg/dl or 3.4–12.0 mmol/l

Protein Metabolism – Nitrogen Metabolism and The Urea Cycle:

The interconversion of amino acids, mainly through transamination reactions **catalysed by aminotransferases,** is essential to balancing the requirements for protein synthesis, while in protein catabolism the amino nitrogen must be removed in the form of ammonia (ammonium) and converted to urea for excretion by the kidneys. Most amino acids are glucogenic, meaning that their carbon skeletons (ketoacid) can be converted to glucose through gluconeogenesis.

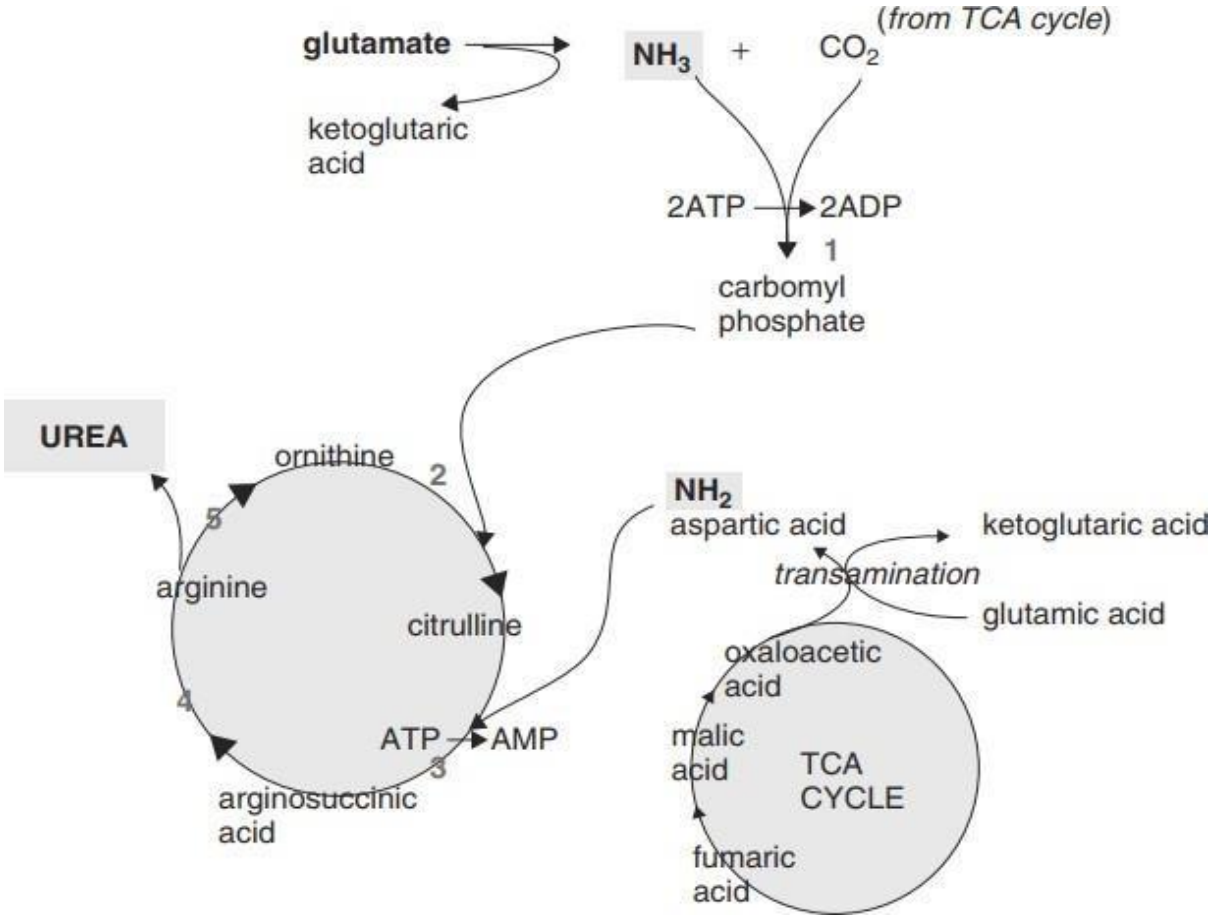
There are specific aminotransferases for all amino acids, except threonine and lysine, and they are particularly abundant in the liver. Alanine transaminase (ALT) and aspartate transaminase (AST) are used as clinical markers of tissue damage. ALT has an important function in the delivery of skeletal muscle carbon and nitrogen (in the form of alanine) to the liver. In skeletal muscle, pyruvate is transaminated to alanine, thus affording an additional route of nitrogen transport from muscle to liver. In the liver, ALT transfers the ammonia to α-ketoglutarate and regenerates pyruvate. The pyruvate can then be diverted into gluconeogenesis. This process is referred to as the glucose–alanine cycle. In peripheral tissues, two enzymes, namely glutamate dehydrogenase and glutamine synthetase, are important in the removal of reduced nitrogen, and particularly so in the brain, which is highly susceptible to free ammonia.



The urea cycle:

The urea cycle is responsible for the excretion of some 80% of the body's excreted nitrogen in the form of urea; this is generated in the liver. Regulation of the urea cycle:

The urea cycle operates only to eliminate excess nitrogen. On high-protein diets the carbon skeletons of the amino acids (keto acids) are oxidized for energy or stored as fat and glycogen, but the amino nitrogen must be excreted. To facilitate this process, urea-cycle enzymes are closely controlled at the gene level. With long-term changes in the quantity of dietary protein, changes of 20-fold or greater in the concentration of cycle enzymes are observed. Under conditions of starvation, enzyme levels rise as proteins are degraded and amino acid carbon skeletons are used to provide energy, thus increasing the quantity



of nitrogen that must be excreted.

Cirrhosis of the liver

Cirrhosis of the liver is the third most common cause of death, after heart disorders and cancer, among the 45–65 age group. Cirrhosis has many possible causes, sometimes more than one cause is present in the same patient. In the Western world, chronic alcoholism and hepatitis C are the most common causes.

LIVER FUNCTION TESTS

1. Write a short note on liver function tests.

Liver function tests: They are tests done to assess the functional capacity of liver (Table 1,3).

Functions of liver:

- Metabolism: Carbohydrates, lipids and proteins
- Excretion: Bilirubin, bile acids and bile salts
- Synthesis: Albumin, α- and β-globulins, clotting factors, cholesterol, lipoprotein
- Storage: Glycogen, vitamins (A, D, B12), etc.
- Detoxification and drug metabolism.

Liver function tests are used to:

- Detect and diagnose liver disease
- Evaluate the severity of liver disease
- Monitor response to therapy
- Assess prognosis of liver disease.

Table 1:(liver function tests).

Class	Tests
Tests based on **excretory** function	Estimation of serum/urine bilirubin, bromsulfthalein
Tests based on **serum enzymes (indicator of liver damage/cholestasis)**	Estimation of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT)
Tests based on **synthetic** functions	Total proteins, serum albumin, globulin, albumin globulin ratio, prothrombin time
Tests based on **detoxification**	Hippuric acid test, blood ammonia

Table 2:(important liver function tests).

Tests	Normal range	Methods	Clinical utility
Total bilirubin	0.2–0.8 mg/dL	van den Bergh reaction	Helps in diagnosis of jaundice
Direct bilirubin	0.1–0.2 mg/dL	van den Bergh reaction	↑ in hepatic and obstructive jaundice
Indirect bilirubin	0.2–0.6 mg/dL	Total bilirubin – direct bilirubin	↑ in hemolytic jaundice
ALT	5–40 U/L	Enzymatic method	↑ in liver damage (e.g. hepatitis)
AST	5–40 U/L	Enzymatic method	↑ in liver damage (e.g. hepatitis)
ALP	40–140 U/L	Enzymatic method	↑ in obstructive jaundice
Total protein	6–8 g/dL	Biuret	↓ in cirrhosis of liver
Albumin	3.5–5 g/dL	Biuret	↓ in cirrhosis of liver
Globulin	2–3.5 mg/dL	Total protein – albumin	↑ in multiple myeloma, ↓ in HIV infection

HIV, human immunodeficiency virus; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; ↑ = increased; ↓ = decreased.

Table 3:(other tests with uses).

Tests	Normal range	Clinical utility
γ-glutamyl transferase (GGT)	10–50 U/L	↑ in alcoholic hepatitis and obstructive jaundice
Prothrombin time	< 14 second	↑ in hepatocellular disease
Plasma ammonia	25–94 µg/dL	↑ in severe hepatocellular disease
Alfa-fetoprotein (AFP)	< 15 ng/mL	↑ in germ cell tumor, ↑ in maternal serum in neural tube defect in fetus

↑ = increased; ↓ = decreased

2. Explain the biochemical findings in blood, urine and feces in different types of jaundice.

Definition: Jaundice is defined as yellowish discoloration of skin, nail beds and sclera. It is caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood. When bilirubin concentration is more than 1 mg/dL, the condition is called hyperbilirubinemia. At a concentration of more than 2 mg/dL, bilirubin diffuses into tissues, which then becomes yellow, leading to jaundice or icterus.

Classification:

Jaundice is classified into three major types:

i. **Prehepatic (hemolytic):** Due to excessive hemolysis, bilirubin production exceeds the capacity of liver toconjugate it.

ii. **Hepatic:** Impaired uptake, conjugation or excretion of bilirubin.

iii. **Postherpetic (obstructive):** Caused by an obstruction in the biliary tract (Table 4).

Table 4: (Classification and findings in jaundice)

Type of jaundice	Causes	Serum bilirubin	Urine and feces	Serum ALT and AST	Serum ALP
Prehepatic [MN: MARS]	**M**alaria **A**utoimmune hemolytic anemia **R**h incompatibility **S**ickle cell anemia	↑ unconjugated bilirubin	• ↑ urobilinogen • Bilirubin negative • ↑ stercobilinogen	Normal or slight ↑	Normal or slight ↑
Hepatic	Hepatitis	↑ conjugated and ↑ unconjugated bilirubin	• Bilirubin present (if microobstruction) • ↓ urobilinogen (if microobstruction)	Markedly elevated	Normal or slight ↑
Post-hepatic	Gallstones Pancreatic tumor Cholangiocarcinoma	↑ conjugated bilirubin	• Urobilinogen absent • Bilirubin present • Clay-colored stool	Normal or slight ↑	Markedly elevated

↑ = increased; ↓ = decreased

3. **Congenital hyperbilirubinemia.**

Definition: A group of hereditary disorders of bilirubin metabolism due to defect in uptake, conjugation or secretionof bilirubin.

Renal Functions and Renal Functions Tests

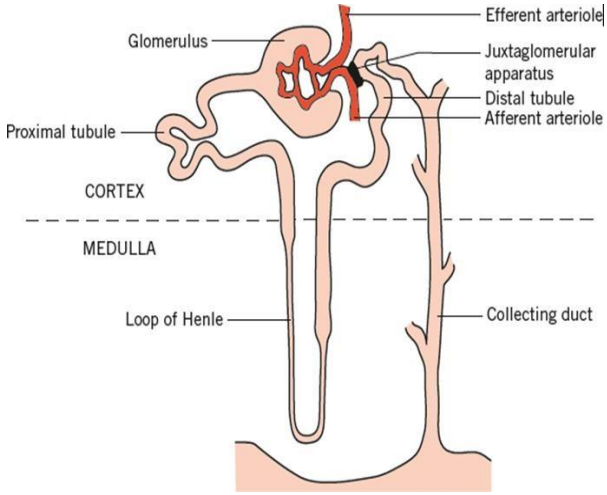
Lecturers 12, 13,14

Kidney:

The kidneys excrete metabolic waste products, and have an essential homeostatic function in that they control the body solute and water status and the acid–base balance. There are about one million nephrons per kidney, each of which is made up of five main functional segments.

The glomeruli, in the cortex of the kidney, surround by a capillary network of blood vessels derived from the afferent, and draining into the efferent, arterioles. Small molecules and water are passively filtered during the passage of blood through these capillaries, the ultrafiltration passing through the vessel walls and the glomerular membranes into the glomerular spaces (Bowman's capsules).

The proximal convoluted tubules, also in the cortex, receive filtrate from the glomerular spaces. Convolution increases the tubular length and therefore contact between the luminal fluid and the proximal tubular cells. The loops of Henle extend down into the renal medulla and ascend again after forming the loop.



The distal convoluted tubules, situated in the cortex, are important for fine adjustment of luminal fluid. They lie near the afferent arterioles, with the juxtaglomerular apparatus between them. The enzyme renin is produced by the latter and its release is controlled by local blood flow.

The collecting ducts start as the distal tubules lead down into the medulla and end by opening into the renal pelvis. The modified fluid from the original filtrate flows from the collecting ducts into the renal tract.

RENAL TUBULAR FUNCTION

Changes in filtration rate alter the total amount of water and solute filtered, but not the composition of the filtrate. From the 200 L of plasma filtered daily, only about 2 L of urine are formed. The composition of urine differs markedly from that of plasma, and therefore of the filtrate. The tubular cells use adenosine triphosphate dependent (ATP) active transport, sometimes selectively, against physicochemical gradients. Transport of charged ions tends to produce an electrochemical gradient that inhibits further transport. This is minimized by two processes.

Isosmotic transport This occurs mainly in the proximal tubules and reclaims the bulk of filtered essential constituents. Active transport of one ion leads to passive movement of anion of the opposite charge in the same direction, along the electrochemical gradient. The movement of sodium (Na^+) depends on the availability of diffusible negatively charged ions, such as chloride (Cl^-). The process is ‘isosmotic’ because the active transport of solute causes equivalent movement of water reabsorption in the same direction. Isosmotic transport also occurs to a lesser extent in the distal part of the nephron.

Ion exchange This occurs mainly in the more distal parts of the nephrons and is important for fine adjustment after bulk reabsorption has taken place. Ions of the same charge, usually cations, are exchanged and neither electrochemical nor osmotic gradients are created.

Clinical and biochemical features of renal disease

Different parts of the nephrons are in close anatomical association and are dependent on a common blood supply.Renal dysfunction of any kind affects all parts of the nephrons to some extent, although sometimes eitherglomerular or tubular dysfunction is predominant. The net effect of renal disease on plasma and urine depends on the proportion of glomeruli to tubules affected and on the number of nephrons involved, first with a lowglomerular filtration rate (GFR) and normal tubular function, and then with tubular damage but a normal GFR. **Uraemia** is the term used to describe a raised plasma urea concentration and is almost always accompanied by an elevated creatinine concentration: usually referred to as azotemia (a raised nitrogen concentration).

Reduced glomerular filtration rate with normal tubular function.
the findings in venous plasma and urine from the affected nephrons will be as follows.

Plasma
- High urea (uraemia) and creatinine concentrations.
- Low bicarbonate concentration, with low pH (acidosis).
- Hyperkalaemia.
- Hyperuricaemia and hyperphosphataemia.

Urine
- Reduced volume (oliguria).
- Low (appropriate) sodium concentration – only if renal blood flow is low, stimulating aldosterone secretion.
-High (appropriate) urea concentration and therefore a high osmolality – only if ADH secretion is stimulated.

Reduced tubular function with normal glomerular filtration rate
Thus, the findings in venous plasma and urine from the affected nephrons will be as follows.

Plasma
- Normal urea and creatinine concentrations (normal glomerular function).

Due to proximal or distal tubular failure:
- low bicarbonate concentration and low pH,
- hypokalaemia.

Due to proximal tubular failure:
- hypophosphataemia, hypomagnesaemia and hypouricaemia.

Urine

Due to proximal and/or distal tubular failure:

- increased volume,
- pH inappropriately high compared with that in plasma.

Due to proximal tubular failure:

- generalized amino aciduria,
- phosphaturia,
- glycosuria.

Acute kidney injury

In adults, **oliguria** is defined as a urine output of less than 400 mL/day, or less than 15 mL/h; it usually indicates a low GFR and a rapid decline in renal function over hours to weeks, with retention of creatinine and nitrogenous waste products. Oliguria may be caused by the factors discussed below.

1- Acute oliguria with reduced GFR (pre-renal)

This is caused by factors that reduce the hydrostatic pressure gradient between the renal capillaries and the tubular lumen. A low intracapillary pressure is the most common cause. It is known as ***renal circulatory insufficiency*** (‘pre-renal uraemia’) and may be due to:

- intravascular depletion of whole blood (haemorrhage) or plasma volume (usually due to gastrointestinal loss), orreduced intake,
- reduced pressure as a result of the vascular dilatation caused by ‘shock’, causes of which include myocardialinfarction, cardiac failure and intravascular haemolysis, including that due to mismatched blood transfusion.

2- Acute oliguria due to intrinsic renal damage

This may be due to:

- prolonged renal circulatory insufficiency,
- acute glomerulonephritis, usually in children
- the history of a sore throat and the finding of red cells in the urine usually make the diagnosis obvious,
- septicaemia, which should be considered when the cause of oliguria is obscure,
- ingestion of a variety of poisons or drugs,
- myoglobulinuria,
- Bence Jones proteinuria.

3- **Acute oliguria due to renal outflow obstruction (postrenal)**

Oliguria or anuria (absence of urine) may occur in post-renal failure. The cause is usually, but not always,clinically obvious and may be due to the following:

- ***Intrarenal obstruction***, with blockage of the tubular lumina by haemoglobin, myoglobin and, very rarely, urateor calcium.
- ***Extrarenal obstruction***, due to calculi, neoplasms, for example prostate or cervix, urethral strictures or prostatichypertrophy, any of which may cause sudden obstruction.

Chronic kidney disease

Chronic renal dysfunction [defined as being reduced eGFR (estimated GFR), proteinuria, haematuria and/or renal structural abnormalities of more than 90 days' duration] is usually the end result of conditions such as diabetes mellitus, hypertension, primary glomerulonephritis, autoimmune disease, obstructive uropathy, polycystic disease, renal artery stenosis, infections and tubular dysfunction and the use of nephrotoxic drugs. It is common, perhaps affecting about 13% of the population. Acute or chronic renal dysfunction can occur when angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are given to patients with renal artery stenosis; a clue to this is an increase in plasma creatinine of about 20 % and/or a decrease in eGFR of about 15 % soon after initiation of the drug.

NEPHROTIC SYNDROME

The nephrotic syndrome is caused by increased glomerular basement membrane permeability, resulting in protein loss, usually more than 3 g a day (or a urine protein to creatinine ratio of > 300 mg/mmol), with consequent hypoproteinaemia, hypoalbuminaemia and peripheral oedema. All but the highest molecular weight plasma proteins can pass through the glomerular basement membrane. The main effects are on plasma proteins and are associated with hyperlipidaemia and hyperfibrinoginaemia. Uraemia occurs only in late stages of the disorder, when many glomeruli have ceased to function.

This comprises reduced eGFR, oedema, hypertension and proteinuria with significant haematuria. It is usually associated with systemic disease such as

postinfectious glomerulonephritis, e.g., post-streptococcal or immunoglobulin A (IgA) nephropathy, ANCA associated vasculitis, e.g., Wegener's granulomatosis or microscopic polyarteritis, or antiglomerular basement membrane disease (Goodpasture's disease).

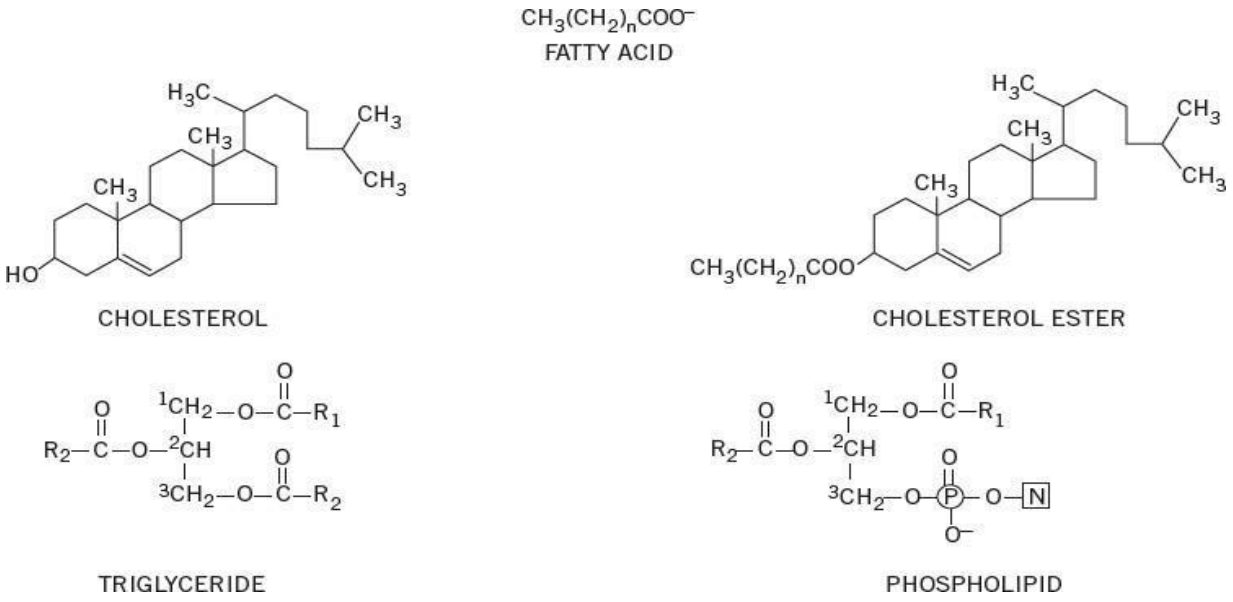
Disorders of Lipid Metabolism

Lectures 14, 15

Lipids are defined as organic compounds that are poorly soluble in water but miscible in organic solvents. Lipids play a critical role in almost all aspects of biological life – they are structural components in cells and are involved in metabolic and hormonal pathways. The importance of having a knowledge of lipid disordersassociated with atherosclerosis such as coronary heart disease.

PLASMA LIPIDS

The chemical structures of the four main forms of lipid present



FATTY ACIDS

These are straight-chain carbon compounds of varying lengths. They may be saturated, containing no double bonds, monounsaturated, with one double bond, or polyunsaturated, with more than one double bond. Fatty acids can esterify with glycerol to form triglycerides or be non-esterified (NEFAs) or free.

TRIGLYSERID

Triglycerides are transported from the intestine to various tissues, including the liver and adipose tissue, as lipoproteins. Following hydrolysis, fatty acids are taken up, re-esterified and stored as triglycerides. Plasma triglyceride concentrations rise after a meal, unlike that of plasma cholesterol.

PHOSPHOLIPIDS

Phospholipids are complex lipids, similar in structure to triglycerides but containing phosphate and a nitrogenous base in place of one of the fatty acids.

CHOLESTEROL

Cholesterol is a steroid alcohol found exclusively in animals and present in virtually all cells and body fluids. It is a precursor of numerous physiologically important steroids, including bile acids and steroid hormones.

LIPOPROTEINS

Because lipids are relatively insoluble in aqueous media, they are transported in body fluids as, often spherical soluble protein complexes called lipoproteins.

Lipoproteins can be classified into five main groups. The first three are triglyceride rich and, because of their large size, they scatter light, which can give plasma a turbid appearance (lipidemic) if present in high concentrations:

- **Chylomicrons** are the largest and least dense lipoproteins and transport exogenous lipid from the intestine to all cells.

- **Very low-density lipoproteins (VLDLs)** transport endogenous lipid from the liver to cells.

- **Intermediate-density lipoproteins (IDLs)**, which are transient and formed during the conversion of VLDL to low-density lipoprotein (LDL), are not normally present in plasma.

The other two lipoprotein classes contain mainly cholesterol and are smaller in size:

- **Low-density lipoproteins are formed from VLDLs** and carry cholesterol to cells.

- **High-density lipoproteins (HDLs)** are the densest lipoproteins and are involved in the transport of cholesterol from cells back to the liver (reverse cholesterol transport).

Clinical significance of lipid fractionation:

Disorder of plasma lipoprotein is called **dyslipoprotenemia.** Dyslipoprotenemia include hyperlipoproteinemin and hypolipoprotenemia.

I) **Hyperlipoproteinemia** (also called hyper lipidemia): The condition of elevation of one or more lipoprotein fraction in the plasma is known as hyperlipoprotenemia. According to Frederickson 's

classification there are 5 types of hyperlipoproteinemia

a) **Type-1 hyperlipoproteinemia:**
Metabolic defect: Lipoprotein lipase enzyme deficiency. Plasma chylomicron and VLDL (Plasma TG level) level are increased) increases.

b) **Type-II a hyperlipoproteinemia (or Familial hypercholesterolemia):**
Metabolic defect: LDL receptor deficiency. Plasma LDL cholesterol is increased.

c) **Type** II **b hyperlipoproteinemia:**
Defect: Overproduction of apo B. Both LDL and VLDL increases. Both plasma TG

and cholesterol level increases.

d) Type III **hyperlipoproteinemia:** Increase in IDL

e) Type IV **hyperlipoproteinemia:** Increase in VLDL

f) Type V hyperlipoproteinemia: Increase in VLDL & chylomicron

II) Hypolipoproteinemia:

Condition of decreased lipoprotein fraction is termed as hypolipoproteinemia.

a) Familial hypolipoprotenemia:

Defect: Failure in the synthesis of apo B lipoproteins. LDL level increases in the blood.

b) Abeta lipoprotenemia:

Defect: Absence of Apo B100. LDL fraction is completely absent.

c) Familial α-lipoprotein deficiency (Tangier disease):

Defect: HDL deficiency, due to reduction in Apo A synthesis.

Cholesterol

Normal level of cholesterol in serum is 150-220 mg/ di. Elevated serum cholesterol level is the major risk factor in promoting atherosclerosis.

Hypercholesterolemia and development of atherosclerosis and CHD:

Hypercholesterolemia is mostly associated with increased LDL cholesterol levels. Increased cholesterol level (mainly LDL fraction) leads to the deposition of cholesterol in the intimal side (inner side) of the arteries, resulting in the formation of fibrous plaques and consequent thickening and hardening of arterial wall causing the condition.

Atherosclerosis. Coronary arteries, aorta and cerebral vessels are predominantly affected. The atherosclerotic plaques lead to narrowing of blood vessels. So, the blood flow through them becomes turbulent and there is increased tendency for **clot formation.**

Causes of **Hypercholesterolemia (and atherosclerosis and CHD):**

- **Diabetes mellitus:** *Due to increased cholesterol synthesis since the availability of acetyl CoA* is *increased.*

- **Obstructive jaundice:** *Cholesterol* is *mainly excreted through bile. obstructive jaundice, there* is *anobstruction in the cholesterol excretion through bile, causing hypercholesterolemia.*

- **Hypothyroidism:** *Thyroid hormones play a role in reducing serum cholesterol level. So, cholesterol levelincreases in hypothyroidism.*

- **Nephrotic syndrome:** *in nephrotic syndrome, lipoprotein lipase (which* is *required to clear lipids fromblood) may be lost in the urine.*

- **Familial Hypercholesterolemia (Familial type** II **a hyperlipoproteinemia):** *due to the defect in LDL receptors (required for hepatic cholesterol uptake), cholesterol level increases in blood.*

- **Other risk factors** that alter the serum cholesterol level are heredity, high BP, smoking, obesity, lack of exercise, emotional stress, excess coffee drinking, sucrose consumption.

Heart Functions and Heart Functions Tests
Lectures 16, 17

Heart Diseases include:

- **Myocardial infarction (MI):** also known as "heart attack," is caused by decreased or complete cessation of blood flow to a portion of the myocardium. Myocardial infarction may be "silent" and go undetected, or it could be a catastrophic event leading to hemodynamic deterioration and sudden death. Most myocardial infarctions are due to underlying coronary artery disease.

- **Cardiac arrest:** is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If correctivemeasures are not taken rapidly, this condition progresses to sudden death.

- **Atherosclerosis:** is a chronic inflammatory disease in which there is a buildup of plaques inside arteries. Atherosclerosis mainly develops through the continuous process of arterial wall lesions due to lipid retention by trapping in the intima by a matrix such as proteoglycans resulting in a modification which, in turn, aggravates chronic inflammationat vulnerable sites in the arteries and plays an important role at all phases of the atherogenic progression.

- **Angina:** is chest pain or discomfort caused when heart muscle doesn't get enough oxygen-rich blood. It may feel like pressure or squeezing in chest.

Cardiac biomarkers are substances that are released into the blood when the heart is damaged or stressed. Measurements of these biomarkers are used to help diagnose acute coronary syndrome (ACS) and cardiac ischemia, conditions associated with insufficient blood flow to the heart.

- Tests for cardiac biomarkers can also be used to help determine a person's risk of having these conditions or to help monitor and manage someone with suspected ACS and cardiac The root causes of both acute coronary syndrome (ACS) and cardiac ischemia are **usually** the buildup of plaque in artery walls and hardening of the arteries (atherosclerosis).
- This can result in severe narrowing of the arteries leading to the heart or a sudden

blockage of blood flow through these coronary arteries ischemia.

- Cardiac ischemia is caused when the supply of blood reaching heart tissue is not enoughto meet the heart's needs.

- When blood flow to the heart is blocked or significantly reduced for a longer period of time (usually for morethan 30-60 minutes), it can cause heart cells to die and is called an acute myocardial infarction (AMI or heart attack).

Cardiac biomarkers What is this test? Biomarkers of myocardial injury:

This test measures the levels of cardiac biomarkers in the blood. These markers
include enzymes, hormones, and proteins (LDH, GOT, CK, cardiac troponin, myoglobin, other markers) .

1. Lactate dehydrogenase isoenzymes:

were used widely in the past for diagnosis of myocardial infarction, but more recently, due to (LDH)-1 availability of troponin immunoassays, lactate dehydrogenase isoenzyme assay has been mostly discontinued in the clinical setting for diagnosis of myocardial infarction. Briefly, LDH exists in five isoenzymes forms (LDH1 , LDH2, LDH3, LDH4, and LDH5) Usually LDH isoenzymes levels increase 24–72 hours following myocardial infarction and reach a peak concentration in 3–4 days. The levels remain elevated for 8 to 14 days, making it a late marker for myocardial infarction. concentration can be elevated in hemolytic anemia, stroke, pancreatitis, ischemic cardiomyopathy, and a variety of other diseases.

2. GOT (glutamate oxaloacetate transaminase) : The first biomarker used to aid in the diagnosis of acute MI was GOT, also called aspartate aminotransferase (AST). The GOT released from cardiomyocytes undergoing necrosis would be useful in diagnosing acute MI

3-Creatine kinase: is an enzyme found primarily in heart muscle cells. There are three isoforms are calledisoenzymes:

- a-CK-MM (found in skeletal muscles and the heart)
- b-CK-MB (found mostly in the heart, but small amounts found in skeletal muscles).
- c-CK-BB (found mostly in the brain and smooth muscle

4- Myoglobin: The small heme protein that assists in oxygen transport in all muscle

tissues, is released within 1 -4 hour and rises more rapidly than Troponin or CK-MB. peaks in nearly 8 to 10 hours, and returns to normal within 24 hours.

5-Troponins: The troponins are a complex of 3 protein subunits, namely troponin C, troponin T and troponin I,located on the thin filaments of the skeletal and cardiac muscle fibers. Troponin C is the calcium-binding component, troponin T is the tropomyosin-binding component and troponin I is the inhibitory component. As the isoforms of troponin C is identical in the skeletal and cardiac muscle, troponin C is not extremely specific for myocardialinjury. Troponin I is extremely specific for the cardiac muscle and has not been isolated from the skeletal muscle. This absolute specificity makes it an ideal marker of myocardial injury.

Pancreatic Functions and Pancreatic Functions Tests

Lectures 18

Pancreas:

Pancreas is only second in size to the liver, weighing about 70–105 g. It is located behind the peritoneal cavity across the upper abdomen at about the level of the first and second lumbar vertebrae, about 1–2 inches above the umbilicus. It is located in the curve made by theduodenum.

The pancreas is composed of two morphologically and functionally different tissues: endocrine tissue and exocrine tissue The endocrine (hormone-releasing) component is by far the smaller of the two and consists of the islets of Langerhans, which are well-delineated, spherical or ovoid clusters composed of at least four different cell types. The islet cells secrete at least four hormones into the blood: insulin, glucagon, gastrin, and somatostatin. The larger, exocrine pancreatic component (enzyme-secreting) secretes about 1.5–2 L/day of fluid, which is rich in digestive enzymes, into ducts that ultimately empty into the duodenum.

The digestive enzymes

(1) the proteolytic enzymes as trypsin and chymotrypsin.
(2) lipid-digesting enzymes as lipase.
(3) pancreatic amylase.

Tests of pancreatic function

- pancreatic function may be suspect when there is evidence of increased amylase and lipase.

Fecal Fat Analysis

- Fecal Fat Analysis.
- Fecal lipids are derived from four sources: unabsorbed ingested lipids, lipids excreted into the intestine (predominantly in the bile), cells shed into the intestine, and metabolism of intestinal bacteria.
- Quantitative Fecal Fat Analysis
- The definitive test for steatorrhea is the quantitative fecal fat determination, usually on a 72-hour stoolcollection, although the collection period may be increased to up to 5 days.
- Sweat Electrolyte Determinations.

Blood Proteins
Lectures 19 and 20

Blood proteins: Proteins are the main and most abundant constituents of the blood serum or plasma, having many essential physiological functions. The most of proteins present in the blood are biochemically not pure; usually, they are a mixture of simple proteins combined with other substances: glycoproteins, lipoproteins, and other conjugated proteins.Proteins have a specific intra-molecular structure and amphoteric nature, containing the balanced portions of hydrophilic and hydrophobic groups.

How is blood plasma different from serum

- Plasma is fluid portion of whole blood, and it is obtained when whole blood containing anti-coagulant is centrifuged, Plasma contains clotting factors.
- Serum is fluid portion of clotted blood, and it is obtained after centrifuging clotted blood. Serum does not contain clotting factors that are normally present in plasma.

Total Protein

Total Protein" in plasma is made up of Albumin and Globulins. Clinical Biochemistry labs routinely measures Total Protein and Albumin usually in serum.
Globulin fraction = Total protein – Albumin
Other plasma proteins (e.g., Immunoglobulin's) are measured as Classes. Immunochemical methods are used to measuring specific plasma proteins, hormones or enzymes.Electrophoresis can be used to separate protein components

Principal plasma proteins		
Class	**Protein**	**Approximate mean serum concentration (g/L)**
	prealbumin	0.25
	albumin	40
α_1-globulin	α_1-antitrypsin	2.9
	α_1-acid glycoprotein	1.0
α_2-globulin	haptoglobins	2.0
	α_2-macroglobulin	2.6
	caeruloplasmin	0.35
β-globulin	transferrin	3.0
	low density lipoprotein	1.0
	complement components (C3)	1.0
γglobulins	IgG	14.0
	IgA	3.5
	IgM	1.5
	IgD	0.03
	IgE	trace

What are the functions of proteins:

- Blood clotting factors: proteins in coagulation cascade.
- Immune defense: Immunoglobulin's, Complement proteins involved in inflammatory responses:
  - Acute phase response proteins: C-reactive protein, alpha-acid glycoprotein.
  - Transport /binding proteins: Albumin, Caeruloplasmin, Haptoglobin, Retinol-binding protein, Sex hormone-binding globulin, Thyroid hormone- binding protein, Transferrin.

What are some of the functions of Albumin?

- Albumin is one of the major plasma proteins; it is synthesized and secreted by the Liver, theBiological half-life of Albumin in plasma: 20 days.
- What are some of the possible causes of Hypoalbuminemia?
- Albumin, the most abundant plasma protein, makes the major contribution (about 80%) to the oncoticpressure of plasma.
- hypoalbuminaemic states, the decreased plasma oncotic pressure disturbs the

equilibrium betweenplasma and interstitial fluidis seen clinically as edema

- Hyperalbuminemia: can be either an artifact, for instance as a result of venous stasis during blood collection or over-infusion of albumin, or be a result of dehydration.

Globulin

- Globulin fraction includes hundreds of serum proteins including carrier proteins, enzymes, complement, andimmunoglobulins.
- Globulins are divided into four groups by electrophoresis.

The four fractions are α1, α2, β and γ, depending on their migratory pattern between the anode and the cathode:

- Increases in the globulin fraction usually result from an increase in immunoglobulins, but there can bean increase in other proteins in pathologic states that have characteristic electrophoretic patterns
- decrease in total globulins due to decreased synthesis, and nephrotic syndrome can cause a decrease due toprotein loss through the kidney.

α- globulin:

1. α1 fraction: consists mainly of α1 antitrypsin. Significant decreases of this fraction are seen in patients with congenital α1 antitrypsin deficiency; an increase is seen in acute inflammatory disordersbecause α1 antitrypsin is an acute phase reactant.
2. α2region: include α2 macroglobulin and haptoglobin. There is an increase in α2 macroglobulin in the nephrotic syndrome when lower molecular weight proteins are lost in the urine. Haptoglobin rises in response to stress, infection, acute inflammation, or tissue necrosis, probably by stimulation of synthesis.

β- globulin:

- Increased β- globulin proteins may indicate:
  - A disorder in which the body has problems breaking down fats (for example, hyperlipoproteinemia, familialhypercholesterolemia)

- Decreased β- globulin proteins may indicate:
  - Abnormally low level of LDL cholesterol malnutrition

γ –region Globulin:

- γ region: The most frequent abnormalities in the γ region are a broad-based polyclonal increase or a narrow monoclonal spike. Polyclonal increases are seen in chronic infections. Monoclonal spikes suggest multiple myeloma, lymphoma. hypogammaglobulinemia is characterized by a decrease in the γ component. It is seen in congenital immune deficiency syndromes.

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