Republic of Iraq

Ministry of Higher Education and Scientific Research

Al-Furat Al-Awsat Technical University

College of Health and Medical Techniques / Kufa

Department of Medical Laboratory Technical

Disorder Metabolic

اسم المادة	لغة التدريس	السنة الدراسية	عدد الساعات الاسبوعيـــــــــــــــــة			
			نظري	عملي	المجموع	عدد الوحدات
اضطرابات الأيض	الانكليزية	الثالثـــة \ الكورس الثاني	2	4	6	4
Metabolic Disorder						

Second Semester (Metabolic Disorder)	
WEEK	**COURSE TOPICS**
1,2	Water and Electrolytes Balance and Imbalance
3,4	Acid Base Balance and Imbalance
5,6	Disorder of Vitamins, Trace Elements and Metals Metabolism
7	Renal Disorder
8	Liver Disorders and Gallstones
9	Pancreatic Disorders
10	Disorders of Lipid Metabolism
11	Metabolic Syndrome
12	Disorder of Protein, Uric Acid, Gout and Purine Metabolism
13,14	Disorders of Haem Metabolism: Iron and the Porphyrias
15	Cardiovascular Disorders

Water and Electrolytes Balance and Imbalance

Distribution of Body Water

Total body water in an adult of 70 kg varies from 60 to 70 per cent (36-49 litres) of total body weight, The body water is distributed mainly in two compartments:

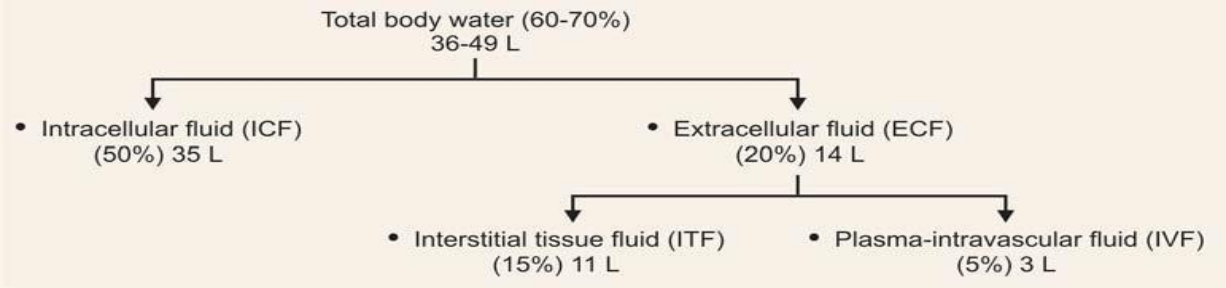
(a) Intracellular fluid (ICF): The fluid present in the cells which is approx. 50 per cent (35 L).

(b) Extracellular fluid ECF: The fluid present outside the cells which constitutes approx. 20 per cent (14 L).

The extracellular fluid (ECF) is considered to be present in the two compartments as follows:

1. Plasma: The fluid present in heart and blood vessels, approx., 5 per cent (3 L) and

2. Interstitial tissue fluid (ITF): 15 per cent (11 L).12`



The extracellular compartment subdivided into four main subdivisions.

1.Plasma volume: This comprises in general the fluid within the heart and blood vessels.

2.Interstitial and lymph fluid: This represents an approximation of the actual fluid environment outside the cells.

3.Fluid of dense connective tissue, cartilage and bones: This includes approx. 4.0 L (7.5 per cent of total body water) and should be considered a “distinct subdivision of ECF”.

4.“Transcellular” fluid: A variety of extracellular fluid collections formed by the “transport” or “secretory activity” of cells. Examples are:

•Fluids found in salivary glands, pancreas, liver and biliary tract, skin, mucous membrane of respiratory and gastro intestinal (GI) tracts; and

•The fluids present in “spaces” within the eyes (aqueous humour), cerebrospinal fluid (CSF) in spinal canal and ventricles of brain, and that within the lumen of GI tract (mostly reabsorbed and not lost).

Intake and Output of Water Balance

During oxidation of foodstuffs, 1 g carbohydrate produces 0.6 mL of water, 1 g protein releases 0.4 mL water and 1 g fat generates 1.1 mL of water. Intake of 1000 kcal produces 125 mL water. The major factors controlling the intake of water are thirst and the rate of metabolism.

The thirst center is stimulated by an increase in the osmolality of blood, leading to increased intake of water. The renal function is the major factor controlling the rate of output of water. The rate of loss through skin is influenced by the weather, the loss being more in hot climate (perspiration) and less in cold climate. Loss of water through skin is increased to 13% for each degree centigrade rise in body temperature during fever.

Intake		Output	
• Fluid by mouth as water and beverages	1000-1500 ml	• Urine (via kidney)	1000-1500 ml
• Water in cooking	700 ml	• Lungs	400 ml
• *Metabolic water*	400 ml	• Skin (insensible perspiration)	600 ml
		• Faeces	100 ml
	Total = 2100-2600 ml		Total = 2100-2600 ml

Electrolytes in the Body

We have less than 100 years of knowledge on role of elements in the human body, it is estimated that 98% of the body mass of man is made up of nine nonmetallic elements. The four main electrolytes namely sodium, magnesium, potassium, and calcium constitute about 1.98 %, while the rest 0.02% or 8.6 g of an average human adults is made up of 10 typical trace elements (chromium, copper, fluorine, iodine, iron, manganese, molybdenum, phosphorus, selenium, and zinc). However, this tiny fraction exerts a tremendous influence on all body functions.

Non-electrolytes, such as glucose, urea, etc. do not dissociate in solution. While substances like NaCl, KCl in solution dissociate into sodium (Na+), potassium (K+) and chloride (Cl–) ions, they are called as electrolytes. Water molecules completely surround these dissociated ions and prevent union of +vely charged particles with –vely charged ones. The +ve ions are called cations and negatively (–vely) charged ions are called anions.

Law of electrical neutrality: Fluid in any body compartment will contain equal number of +vely charged and –vely charged ions.

Inorganic “electrolytes”: Because of the relatively large quantities of these materials in the body, they are by far the most important both in distribution and retention of body water.

Normal Water and Electrolyte Balance

The organs which are constantly regulating the electrolyte levels are the:

(a) GI Tract: About 8 litres of fluid of different electrolytes enter GI tract every day and are reabsorbed almost completely with fluid loss approx. 100 to 150 ml, and electrolyte loss of Na+ approx. 10 to 30 mEq and of K+ approx. 10 mEq

(b) Kidneys: Internal circulation of salts constantly occurring in kidneys is at a much faster rate than that observed in GI tract.

Regulatory Mechanisms

1. In health, the volume and composition of various body fluid compartments are maintained within physiological limits even in the face of wide variations in intake of water and solutes.

2. Osmolarity of ICF is determined mainly by its K+ concentration, while that of ECF by Na+ concentration. The kidneys respond promptly to deviations in osmolarity or individual ions concentration in ECF.

3. Homeostasis of body fluids: Therefore, involves mechanisms that:

- Responds to fluctuations in volume, as well as,
- To changes in concentration of total solutes or of individual ions.

4. Current concepts of the nature of the regulatory mechanisms include the existence of receptors sensitive to variations in:

- Osmolar concentration (osmoreceptors)
- Or individual ions (chemoreceptors) concentration in ECF and,
- To local or general variations in intravascular pressures (baroreceptors)
- And plasma/or ECF volume (volume receptors or stretch receptors)

The intrarenal mechanisms concerned with excretion of water and solutes may be influenced by stimuli initiated in these receptors either:

• **By direct neural connections**: The intake of fluid is regulated by the mechanism of "thirst". A thirst centre is located in III ventricle which regulates the amount of water consumed as water or beverages. A deficient intake of water with continuing "obligatory losses" leads to concentration of body fluids with respect to solutes and a rise in osmotic pressure. This tends to draw water from ICF, the dehydration of the cells seems to be the main stimulus for thirst mechanisms through osmoreceptors as well as sensory nerves of mouth and pharynx (IX and X), which respond to dryness of the mouth and pharynx.

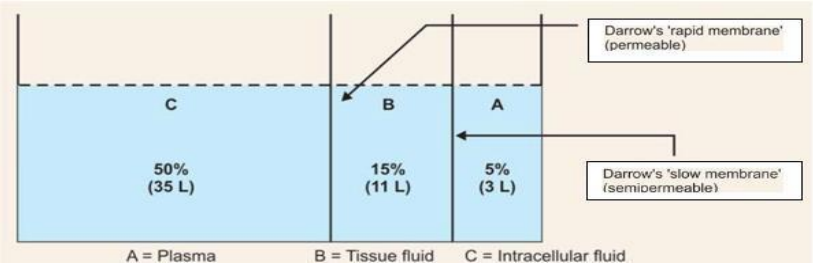
• Through production and release of certain hormones, these are mainly two:

1. Antidiuretic hormone (ADH) or Vasopressin, 2. Aldosterone,

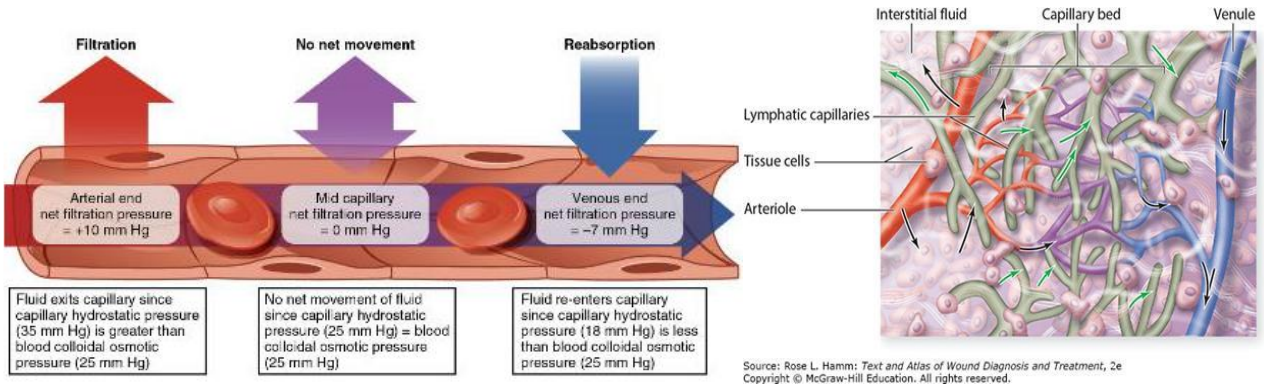
The former regulating the excretion of water and the latter Na+ and K+.

Under normal conditions in health, the relative volumes of water in above three compartments are kept constant. Water can pass freely through the membrane which divide plasma from tissue fluid; and tissue fluid from intracellular fluid; but distribution of water is controlled by the osmotic pressure exerted by substances present in each compartment, i.e. the electrolytes and protein molecules.

• Membrane separating ICF from tissue fluid is Semipermeable called as slow membrane by Darrow, and it allows only passage of water but not electrolytes and protein molecules in health. Normally, there is osmotic equilibrium between these two compartments, but if this is disturbed, water is drawn from the compartment with lower osmotic pressure into that with higher osmotic pressure until equilibrium is restored. The osmotic imbalance between these two compartments results in water being either sucked out of the cells (producing cellular dehydration) or water is drawn into the cells (producing cellular oedema) to restore the balance.



Starling hypothesis: There is also fluid exchange taking place at the 'capillary beds. The mechanism starling hypothesis, provides for a continual circulation of fluid between the capillaries and the tissue spaces, a balance being maintained between the quantity of water filtered and that reabsorbed.



Water and Electrolyte Imbalance

Abnormalities can be two types: Dehydration Due to loss of water, or electrolytes or both and Water intoxication.

Dehydration

Dehydration is a disturbance of water balance in which the output exceeds the intake, causing a reduction of body water below the normal level. there is an accompanying disturbance of electrolytes. Dehydration may be the result of:

• Pure water depletion

• Pure salt depletion

• Mixed type in which both occur.

A. Pure Water Depletion (Primary Dehydration)

Definition: Pure water depletion occurs when water intake is stopped or water intake is inadequate and there is no parallel loss of salt in the secretions from the body.

Causes

• When a patient is too weak or too ill to satisfy his/her water needs,

• In mental patients who refuse to drink,

• In cases of coma, dysphagia (difficulty in swallowing),

• In individuals lost in desert or shipwrecked.

B. Pure Salt Depletion

Definition: Pure salt depletion occurs when fluids of high Na^+ or Cl^- content are lost from the body. The term "sodium depletion" is now used rather than salt depletion, to lay stress on the fact that Na^+ is the significant ion concerned with the maintenance of ECF volume.

Causes

• Loss of Na^+ can occur by excessive sweating, when only water is taken in as replacement.

• Another important means of sodium depletion is loss of GI fluids as in vomiting, diarrhoea, pancreatic/or biliary fistulaes, cholera.

• Urinary losses of Na+ are perhaps not as common, but can occur in such clinical states as Addison's disease, diabetic acidosis and certain instances of chronic renal diseases. In these cases, loss of Na+ may be aggravated by accompanying vomiting.

• Vigorous use of diuretics and low sodium or salt-free diets in the management of congestive heart failure may induce sodium depletion.

C. Mixed Water and Salt (Sodium) Depletion

In clinical practice, depletion of both water and salt (sodium) is more common than depletion of either alone. Definition: Mixed depletion occurs when there is loss of fluids containing high concentration of Na+ and Cl- without a free intake of water.

Water Intoxication

This condition is caused by excess of water retention in the body and can occur due to the following causes:

• Renal failure

• Excessive administration of fluids parenterally.

• Hyper secretion of ADH following the administration of an anaesthetic for surgery, administration of

narcotic drugs or in stress (including any surgery)

• Excess of aldosterone may lead to an overhydration of the body and subsequent water intoxication

(Conn's Syndrome).

Clinically: Headache, nausea, incoordination of movements, muscular weakness and delirium are the main symptoms of water intoxication.

Changes:

• PCV, Hb concentration and plasma proteins concentration are all decreased.

• Plasma electrolytes are lowered

• Urinary volume is usually increased and is of low sp. gravity.

Acid Base Balance and Imbalance

Normal cell metabolism depends on the maintenance of blood pH within very narrow limit (7.35 -7.45). Even relatively mild excursions outside this normal pH range can have deleterious effects, including reduced oxygen delivery to tissues, electrolyte disturbances and changes in heart muscle contractility; survival is rare if blood pH falls below 6.8 or rises above 7.8.

The problem for the body is that normal metabolism is associated with continuous production of hydrogen ions (H^+) and carbon dioxide (CO_2), both of which tend to reduce pH. The mechanism which overcomes this problem and serves to maintain normal blood pH (i.e., preserve acid-base homeostasis) is a complex synergy of action involving chemical buffers in blood, the red cells (erythrocytes), which circulate in blood, and the function of three organs: lungs; kidneys and brain.

Before explaining how these five elements contribute to the overall maintenance of blood pH, it would be helpful to quickly review some basic concepts.

pH

pH is a measure of hydrogen ion concentration [H^+].

pH is a scale of 0-14 of acidity and alkalinity. Pure water has a pH of 7 and is neutral (neither acidic nor alkaline). pH above 7 is alkaline and below 7 acidic. Thus, the pH of blood (7.35-7.45) is slightly alkaline, reserved for blood pH greater than 7.45 and the term acidosis is reserved for blood pH less than 7.35.

Buffer

Definition: a solution which resists the change in pH which might be expected to occur upon the addition of acid or base to the solution. Buffers consist of mixtures of weak acids and their corresponding salts, alternatively, weak bases and their salts. The former type is the more important and common in human body.

• The buffer systems of the blood, tissue fluids and cells; immediately combine with acid or base to prevent excessive changes in hydrogen ion concentration.

• Buffer systems do not eliminate hydrogen ions from the body or add them to the body but only keep them tied up until balance can be re-established.

Blood Buffers:

Various buffer systems present in human body are:

1. Buffers of extracellular fluid present in plasma.

- Bicarbonate buffer ($NaHCO_3/H_2CO_3$).
- Phosphate buffer (Na_2HPO_4/NaH_2PO_4).
- Protein buffer (Na protein/H protein).

Buffer system	*Plasma (extracellular) buffer*	*Erythrocyte (intracellular) buffer*
Bicarbonate	$NaHCO_3/H_2CO_3$	$KHCO_3/H_2CO_3$
Phosphate	Na_2HPO_4/NaH_2PO_4	K_2HPO_4/KH_2PO_4
Protein	Na Protein/ H Protein	KHb/HHb $KHbO_2/HHbO_2$

2. Buffers of intracellular fluid present in erythrocyte are:

- Bicarbonate buffer ($KHCO_3/H_2CO_3$).
- Phosphate buffer (K_2HPO_4/KH_2PO_4).
- Hemoglobin buffer (KHb/HHb), ($KHbO_2/HHbO_2$).

Physiology of acid-base balance: In fact, the lungs ensure removal of carbonic acid (as carbon dioxide CO2) and the kidneys ensure continuous regeneration of bicarbonate.

This role of the lungs is dependent on characteristic of the bicarbonate buffering system and that is the ability of carbonic acid to be converted to carbon dioxide and water, the following equation outlines the relationship of all elements of the bicarbonate buffering system as it operates in the body, it is important to note that the reactions are reversible.

$H^+ + HCO_3^- \leftrightarrow H_2CO_3$ D $\leftrightarrow H_2O + CO_2$

Direction is dependent on the relative concentration of each element. So that, for example, a rise in carbon dioxide concentration force's reaction to the left with increased formation of carbonic acid and ultimately hydrogen ions.

Lung function, transport of CO_2 and acid-base balance

A constant amount of CO_2 in blood, essential for normal acid-base balance, reflects a balance between that produced as a result of tissue cell metabolism and that excreted by the lungs in expired air.

By varying the rate at which carbon dioxide is excreted, the lungs regulate the carbon dioxide content of blood. Carbon dioxide (CO_2) diffuses out of tissue cells to surrounding capillary blood (Fig. 1a), a small proportion dissolves in blood plasma and is transported to the lungs unchanged, but most diffuses into red cells where it combines with water to form carbonic acid. The acid dissociates with production of hydrogen ions and bicarbonate. Hydrogen ions combine with deoxygenated hemoglobin (hemoglobin is acting as a buffer here), preventing a dangerous fall in cellular pH, and bicarbonate diffuses along a concentration gradient from red cell to plasma. Thus, most of the carbon dioxide produced in the tissues is transported to the lungs as bicarbonate in blood plasma.

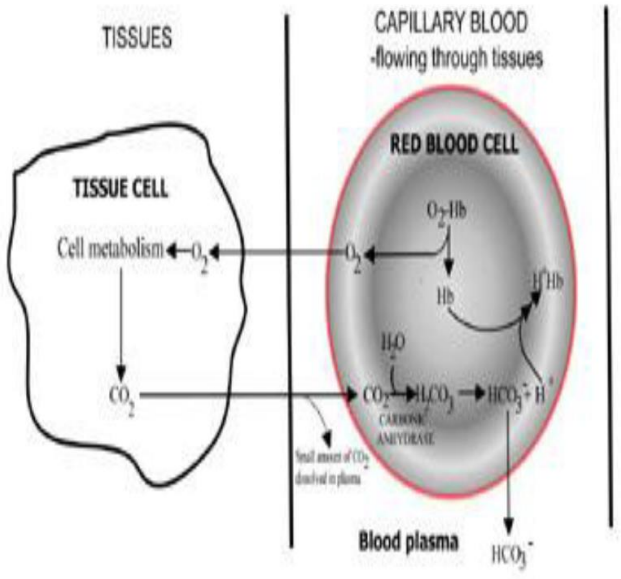


Fig. 1a. CO2 produced in tissues converted to bicarbonate for transport to lungs.

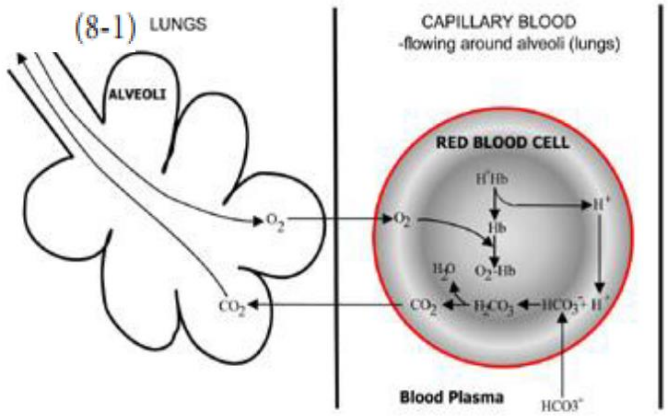


Fig. 1b. At the lungs bicarbonate converted back to CO2 and eliminated by the lungs

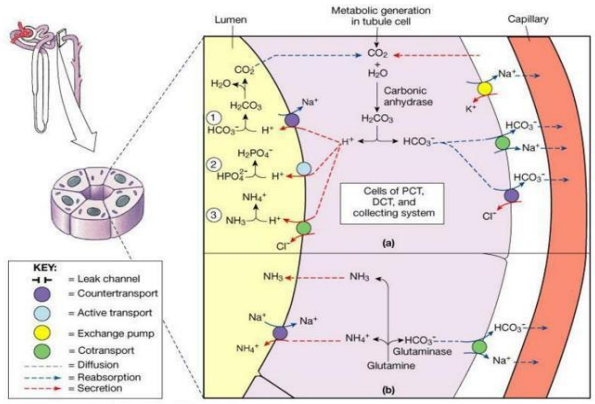
At the alveoli in the lungs the process is reversed (Fig. 1b). Hydrogen ions are displaced from hemoglobin as it takes up oxygen from inspired air. The hydrogen ions are now buffered by bicarbonate which diffuses from plasma back into red cell, and carbonic acid is formed. As the concentration of this rise, it is converted to water and carbon dioxide. Finally, carbon dioxide diffuses down a concentration gradient from red cell to alveoli for excretion in expired air.

Brain and Acid-Base Balance

Respiratory chemoreceptors in the brain stem respond to changes in the concentration of carbon dioxide in blood, causing increased ventilation (breathing) if carbon dioxide concentration rises and decreased ventilation if carbon dioxide falls.

Kidneys and Acid-Base Balance

These two tasks, elimination of hydrogen ions and regeneration of bicarbonate, are accomplished by the kidneys. Renal tubule cells are rich in the enzyme carbonic anhydrase, which facilitates formation of carbonic acid from carbon dioxideand water. Carbonic acid dissociates to bicarbonate and hydrogen ions. The bicarbonate is reabsorbed into blood and the hydrogen ions pass into the lumen of the tubule and are eliminated from the body in urine.



Mechanisms of Regulation of pH

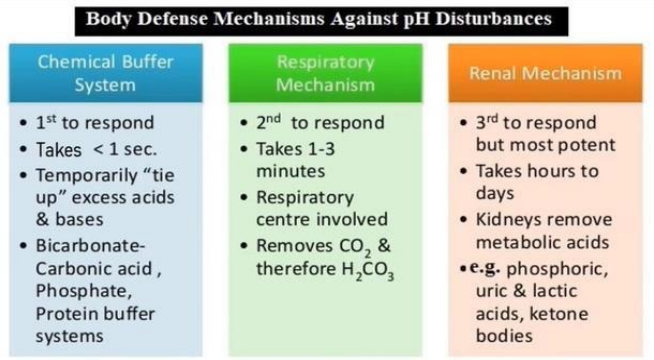
The mechanisms of regulation of blood pH involves the following factors:

(a) “First-line” Defence: They are mainly:

- Buffer systems in the blood
- Respiratory mechanisms:

(b) “Second-line” Defence: This is achieved by kidneys (Renal mechanisms).

(c) Dilution factor



Disturbances of Acid-Base Balance

Most acid-base disturbances result from

• disease or damage to organs (kidney, lungs, brain) whose normal function is necessary for acid-base homeostasis,

• disease which causes abnormally increased production of metabolic acids such that homeostatic mechanisms are overwhelmed.

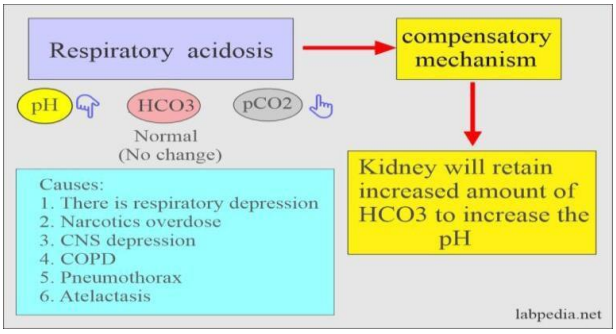
• medical intervention (e.g. mechanical ventilation, some drugs) Arterial blood gases (ABG) are the blood test used to identify and monitor acid-base disturbances. Three parameters measured during blood gas analysis, arterial blood pH, partial pressure of carbon dioxide in arterial blood (pCO_2), concentration of bicarbonate (HCO_3–) are of crucial importance.

Results of these three allow classification of acid-base disturbance to one of four etiological categories:

1. **Respiratory Acidosis – (raised pCO_2, reduced pH)**

Respiratory acidosis is characterized by increased pCO_2 due to inadequate alveolar ventilation (hypoventilation) and consequent reduced elimination of CO_2 from the blood. Respiratory disease, such as bronchopneumonia, emphysema, asthma and Chronic Obstructive Pulmonary Disease (COPD), may all be associated with hypoventilation sufficient to cause respiratory acidosis. Some drugs (e.g., morphine and barbiturates) can cause respiratory acidosis by depressing the respiratory center in the brain.

Damage or trauma to the chest wall and the musculature involved in the mechanics of respiration may reduce ventilation rate. This explains the respiratory acidosis that can complicate the course of diseases such as poliomyelitis, and recovery from severe chest trauma.



2. **Respiratory Alkalosis – (reduced pCO_2, increased pH)**

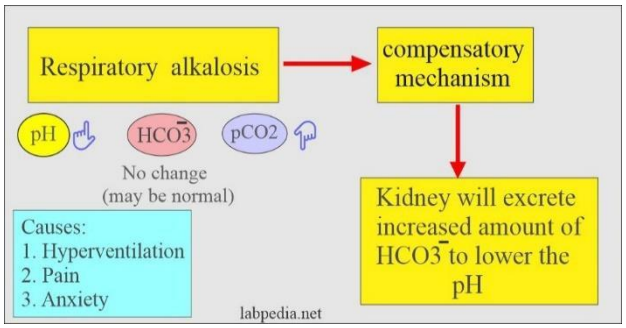
By contrast, respiratory alkalosis is characterized by decreased pCO_2 due to excessive alveolar ventilation and resulting excessive elimination of CO_2 from blood. Disease in which, due to reduced oxygen in blood (hypoxemia), the respiratory center is stimulated can result in respiratory alkalosis.

Examples here include severe anemia, pulmonary embolism and adult respiratory syndrome.

Hyperventilation sufficient to cause respiratory alkalosis can be a feature of anxiety attacks and response to severe pain. One of the less welcome properties of salicylate (aspirin) is its stimulatory effect on the respiratory center. This effect accounts for the respiratory alkalosis that occurs following salicylate overdose.

Primary disturbances of pCO_2 (respiratory acidosis and alkalosis) are compensated for by renal adjustments of hydrogen ion excretion which result in changes in [HCO_3–] that compensate appropriately for primary change in pCO_2. Thus, the renal compensation for respiratory acidosis (raised pCO_2) involves increased reabsorption of bicarbonate, and renal compensation for respiratory alkalosis (reduced pCO_2) involves reduced bicarbonate reabsorption. Respiratory compensation for a primary metabolic disturbance occurs much more quickly than metabolic (renal) compensation for a primary respiratory disturbance. In the second case, compensation occurs over days rather than hours.

If compensation results in return of pH to normal then the patient is said to be fully compensated. But in many cases the compensation returns pH towards normal without actually achieving normality; in such cases the patient is said to be partially compensated. For reasons described above, metabolic alkalosis is very rarely fully compensated.



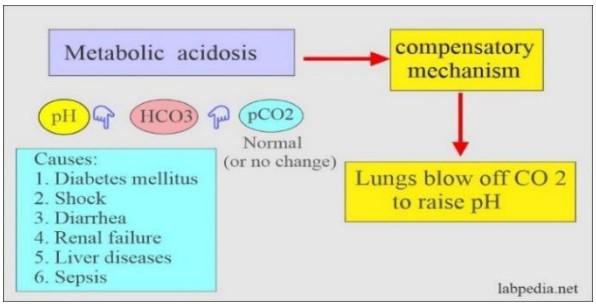
3. Metabolic Acidosis – (decreased HCO_3–, decreased pH)

Reduced bicarbonate is always a feature of metabolic acidosis. Consider the patient with metabolic acidosis whose pH is low because bicarbonate [HCO_3–] is low. To compensate for the low [HCO_3–] and restore the all-important ratio towards normal the patient must lower his pCO_2. Chemoreceptors in the respiratory center of the brain respond to a rising hydrogen ion concentration (low pH), causing increased ventilation (hyperventilation) and thereby

increased elimination of carbon dioxide; the pCO_2 falls and the ratio [HCO_3–]: pCO_2 returns towards normal.

This occurs for one of two reasons: increased use of bicarbonate in buffering an abnormal acid load or increased losses of bicarbonate from the body. Diabetic ketoacidosis and lactic acidosis are two conditions characterized by overproduction of metabolic acids and consequent exhaustion of bicarbonate. In the first case, abnormally high blood concentrations of keto-acids (b-hydroxybutyric acid and acetoacetic acid) reflect the severe metabolic rearrangements which result from insulin deficiency.

All cells produce lactic acid if they are deficient of oxygen, so increased lactic acid production and resulting metabolic acidosis occur in any condition in which oxygen delivery to the tissues is severely compromised. Examples include cardiac arrest and any condition associated with hypovolemic shock (e.g., massive fluid loss). Failure to regenerate bicarbonate and excrete hydrogen ions explains the metabolic acidosis that occurs in renal failure.

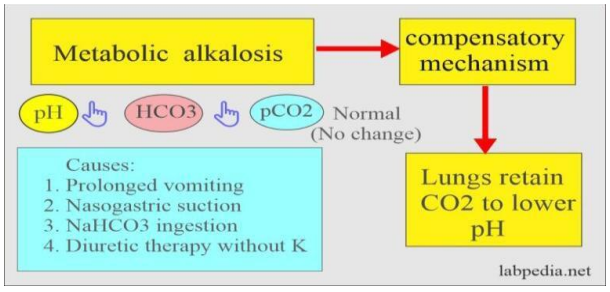


4. Metabolic Alkalosis – (increased HCO –, increased pH)

Bicarbonate is always raised in metabolic alkalosis. Compensation for metabolic alkalosis in which [HCO_3–] is high, by contrast, involve depression of respiration and thereby retention of carbon dioxide so that the pCO_2 rises to match the increase in [HCO_3–]. However, depression of respiration has the unwelcome side effect of threatening adequate oxygenation of tissues. For this reason,

respiratory compensation of metabolic alkalosis is limited. Rarely, excessive administration of bicarbonate or ingestion of bicarbonate in antacid preparation can cause metabolic alkalosis, but this is usually transient. Abnormal loss of hydrogen ions from the body can be the primary problem. Bicarbonate which would otherwise be consumed in buffering these lost hydrogen ions consequently accumulates in blood. Gastric juice is acidic and gastric aspiration or any disease process in which gastric contents are lost from the body represents a loss of hydrogen ions.

The projectile vomiting of gastric juice, for example, explains the metabolic alkalosis that can occur in patients with pyloric stenosis. Severe potassium depletion can cause metabolic alkalosis due to the reciprocal relationship between hydrogen and potassium ions.

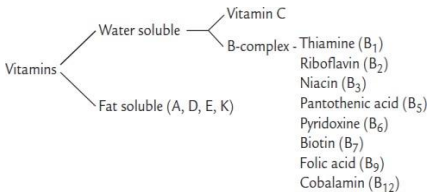


Disorder of Vitamins, Trace Elements and Metals Metabolism

At one time, vitamins were thought to be amines and hence the term 'vitamins' was coined for substances that are essential for life but needed in only minute amounts. Vitamins are now known to be organic compounds nutrients which are essential for normal growth and development and play a central role in metabolism. Most vitamins are either not synthesized or are synthesized in inadequate amounts by the human organism; therefore, they must be obtained from an exogenous source, such as diet or bacterial flora in the gut.

Classification of Vitamins

Vitamins are divided into fat-soluble and water-soluble groups. The fat-soluble vitamins are A, D, E, and K, whereas water-soluble vitamins include B group of vitamins (B1, B2, B3, B5, B6, B7, B12 and folate) and ascorbic acid (vitamin C).



Name	Daily requirement	Deficiency disease	Dietary sources
Water-soluble			
• Vitamin B_1 (Thiamine)	1.0–1.5 mg	Beriberi and Wernicke–Korsakoff syndrome	Legumes, pork, liver, nuts, the germ of cereals, yeast and outer layers of seeds.
• Vitamin B_3 (Niacin)	12–20 mg	Pellagra	Unrefined grains, yeast, liver, legumes and lean meat.
• Vitamin B_2 (Riboflavin)	1.1–1.5 mg	Ariboflavinosis (rare)	Milk, eggs, liver, and green leafy vegetables.
• Vitamin B_6 (Pyridoxine)	1.6–2 mg on a 100 g protein diet	Rare	Whole-grain cereals, wheat, corn, nuts, muscle meat, liver and fish.
• Pantothenic acid	5–10 mg	Rare	Yeast, liver and eggs
• Vitamin B_7 (Biotin)	5 µg/1000 kcal	Rare	Liver, kidney, milk, egg yolk, corn, and soya milk.
• Vitamin B_{12} (Cyanocobalamin)	3 µg	Pernicious anaemia	Liver, kidney, meats and milk
• Folic acid	400 µg	Megaloblastic anaemia	Liver, yeast and green vegetables.
• Vitamin C (Ascorbic acid)	45 mg	Scurvy	Citrus fruits, potatoes, particularly the skin, strawberries, raw or minimally cooked (green) vegetables and tomatoes; amla is the richest source.
Fat-soluble			
• Vitamin A	3500 IU for men 2500 IU for women	Night blindness; skin lesions	Liver, kidney, butter fat, oils, egg yolk, green leafy vegetables, fruits.
• Vitamin D	400 IU (10 µg vitamin D_3)	Rickets in children, osteomalacia in adults	Salt water fish, liver, egg yolk and butter.
• Vitamin E (Tocopherols)	10–30 mg	Liver atrophy, red blood cell haemolysis, neurological disorders	Vegetables, milk, seed oils, liver and eggs.
• Vitamin K	1 µg/kg	Bleeding tendency	Spinach, cabbage, egg yolk.

Water-Soluble

- **Thiamine (B1)**

Functions: Thiamine is a component of thiamine pyrophosphate, which is necessary for the conversion of pyruvate to acetyl-CoA.

Thiamine deficiency: A. In thiamine deficiency, pyruvate cannot be metabolized and accumulates in the blood. Deficiency is usually due to excess ethanol intake with high carbohydrate but poor vitamin intake. One of the commonest causes worldwide is a diet high in un-enriched white flour or rice.

- **Riboflavin (B2)**

Functions: Riboflavin is present in many naturally occurring flavoproteins, in most of which it is incorporated in the form of flavine mononucleotide (FMN) and flavine adenine dinucleotide (FAD). Both FMN and FAD are reversible electron carriers in biological oxidation systems, which are, in turn, oxidized by cytochromes.

Riboflavin deficiency: The causes of riboflavin deficiency include poor intake, malabsorption, alcoholism and increased metabolic rate in severe illness. Riboflavin deficiency (ariboflavinosis) causes a rough, scaly skin, especially on the face, cheilosis (red, swollen, cracked lips. Congestion of conjunctival blood vessels may be visible if the eye is examined with a slit lamp.

- **Nicotinamide (B3 niacin)**

Functions: Nicotinamide is the active constituent of nicotinamide adenine dinucleotide (NAD+) and its phosphate (NADP+), which are important cofactors in oxidation–reduction reactions. Reduced NAD+ and NADP+ are, in turn, re-oxidized by flavoproteins, and the functions of riboflavin and nicotinamide are closely linked. The NAD+ and NADP+ and their reduced forms are essential for glycolysis and oxidative phosphorylation, and for many synthetic processes.

Nicotinamide deficiency: It may be difficult to distinguish between the clinical features due to coexistent deficiencies, such as of pyridoxine, and those specifically due to nicotinamide. However, nicotinamide deficiency is probably the most important factor precipitating the clinical syndrome of pellagra. The mnemonic ‘three Ds’ – dementia, dermatitis, diarrhoea – may help in remembering the symptoms.

- **Pyridoxine (B6)**

Functions: Pyridoxal phosphate, formed in the liver from pyridoxine, pyridoxal and pyridoxamine, is a cofactor mainly for the transaminases, and for decarboxylation of amino acids.

Pyridoxal phosphate deficiency may cause roughening of the skin, peripheral neuropathy and a sore tongue. A rare hypochromic microcytic anaemia, with increased iron stores (sideroblastic anaemia).

- **Folate and vitamin B12**

Function: both folate and vitamin B12 are essential for the normal maturation of erythrocytes;

Folate and vitamin B12 deficiency: deficiency causes macrocytosis or megaloblastic anaemia. Their effects are so closely inter-related that they are usually considered together. clinical deficiency is relatively common in intestinal malabsorption syndromes, especially in the ‘contaminated bowel’ syndrome, all forms are absorbed

mainly in the terminal ileum, combined with intrinsic factor derived from the gastric parietal cells. In pernicious anaemia, antibodies to gastric parietal cells and/or to intrinsic factor cause malabsorption of vitamin B12. Low maternal folate intake is also associated with neural tube defects in the fetus.

- **Ascorbate (vitamin C)**

Functions: ascorbate can be reversibly oxidized in biological systems to dehydroascorbate and, although its functions in humans are not clear, it probably acts as a hydrogen carrier and antioxidant as well as being involved in collagen synthesis.

Ascorbate deficiency: deficiency of ascorbate causes scurvy, which was common on long sea voyages before the 18th century when fresh fruit and vegetables were unavailable. Dehydroascorbate is easily and irreversibly oxidized and loses its biological activity in the presence of oxygen; this reaction is catalysed by heat. Deficiency occurs most commonly in the elderly, especially those who do not eat fresh fruit and vegetables. It can also occur in iron overload.

Fat-Soluble Vitamins

- **Vitamin A (retinol)**

Functions: Rhodopsin (visual purple), the retinal pigment that is necessary for vision in poor light, consists of a protein (opsin) combined with vitamin A. Rhodopsin decomposes in bright light. It is partly regenerated in the dark, but, because this is not quantitatively complete, vitamin A is needed to maintain retinol levels. Vitamin A is also essential for normal mucopolysaccharide synthesis and mucus secretion.

Vitamin A deficiency: hepatic stores of vitamin A are large and therefore clinical signs develop only after many months, or even years, of dietary deficiency. Such prolonged deficiency is very rare in affluent communities. In steatorrhoea, clinical evidence of vitamin A is rare, although plasma concentrations may be low. Deficiency is relatively common in poor countries, especially in children, and can cause blindness.

Hypervitaminosis A: Vitamin A in large doses is toxic. Acute intoxication has been reported in Arctic regions as a result of eating polar bear liver, which has very high vitamin A content. More commonly, overdosage is due to the excessive use of vitamin preparations.

- **Vitamin D (calciferol)**

Functions: Dietary sources are important when requirements are high, such as during growth or pregnancy, or in those elderly or chronically sick individuals who are confined indoors and not exposed to the sun. Vitamin D is transported in plasma bound to specific carrier proteins. It is inactive until metabolized. In the liver, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol (25-OHD_3) by the enzyme 25- hydroxylase. The rate of formation of 25-OHD3 is affected by the supply of substrate in the form of calciferol, whether derived from the skin or from the diet. It is the main circulating form and store of the vitamin. In the proximal renal tubular cells of the kidney, 25-OHD3 undergoes a second hydroxylation, catalysed by the enzyme 1-a-hydroxylase to form the active metabolite 1,25-$(OH)_2D_3$. The activity of 1-a- hydroxylase, and hence the production of 1,25-(OH)2D3, may be stimulated by:

a low plasma phosphate concentration,

an increase in plasma PTH concentration, possibly because of its phosphate-lowering effect. Its activity is inhibited by:

- hyperphosphataemia,

- high levels of free ionized calcium.

The kidney is an endocrine organ, synthesizing and releasing the hormone 1,25-(OH)2D3; impairment of the final hydroxylation helps explain the hypocalcaemia of renal disease. This hormone increases calcium absorption by intestinal mucosal cells. In conjunction with PTH, it stimulates osteoclastic activity, releasing calcium from bone.

The action of PTH on bone is impaired in the absence of 1,25-(OH)2D3. A fall in plasma free ionized calcium concentration stimulates PTH secretion.

The PTH enhances 1-a-hydroxylase activity and therefore stimulates 1,25-(OH)2D3 synthesis. The two hormones act synergistically on the osteoclasts of bone, releasing calcium into the circulation; 1,25-(OH)2D3 also increases calcium absorption from the intestinal lumen. In the short term, the homeostatic mechanisms involving the effects on bone are the more important; if hypocalcaemia is prolonged, more efficient absorption becomes important. Once the plasma free ionized calcium concentration is adjusted, the secretion of both PTH and 1,25-(OH)2D3 is suppressed.

Thus, 25-OHD3 is the circulating, inactive form of vitamin D and plasma concentrations fall in deficiency states. The measurement of the biologically active metabolite, 1,25-(OH)2D3, which circulates in plasma bound to vitamin D-binding protein (VDBP) in very low concentrations, is rarely indicated unless a defect in the vitamin metabolic pathway is suspected, as it does not reflect body stores.

Vitamin D deficiency: as are disorders of bone, including rickets and osteomalacia. In chronic overdosage, stores of cholecalciferol are large and therefore hypercalcaemia may persist, or even progress, for several weeks after ingestion of the vitamin is stopped.

- **Vitamin E (a-tocopherol)**

Vitamin E acts as an antioxidant, and deficiency can have many clinical sequelae.

Vitamin E deficiency: The common causes of vitamin E deficiency are poor intake and fat malabsorption, for example cystic fibrosis. Low plasma concentrations may also be seen in the rare hypo abetalipoproteinemia, in which there are low concentrations of the low-density lipoprotein (LDL) that is involved in carrying some of the fat-soluble vitamins. The clinical features of vitamin E deficiency include increased haemolysis, a possibly increased risk of atherosclerosis and, in low-birthweight babies, retrolental fibroplasias and intraventricular hemorrhages. Vitamin E excess is rare.

- **Vitamin K**

Functions: Vitamin K is needed for the synthesis of prothrombin and coagulation factors VII, IX and X in the liver, and deficiency is accompanied by a bleeding tendency with a prolonged prothrombin time. Clinically, vitamin K is sometimes given to reverse the actions of the anticoagulant warfarin in patients in whom it is causing bleeding problems, as evidenced by a prolonged prothrombin time or international normalized ratio (INR). Vitamin K is also involved in bone mineralization. Vitamin K can be synthesized by bacteria in the ileum, from where it can be absorbed, and thus dietary deficiency is unlikely.

Vitamin K deficiency: may occur,

- in patients with steatorrhoea – the vitamin, whether taken in the diet or produced by intestinal bacteria, cannot be absorbed normally,

- after the administration of some broad-spectrum antibiotics, which may alter the intestinal bacterial flora

In the newborn infant, plasma vitamin K concentrations are lower than in adults because very little can be transported across the placenta, the neonatal gut is only gradually colonized by bacteria capable of synthesizing vitamin K and protein synthesis has not yet reached full adult capacity, particularly in premature infants. Deficiency may be severe enough to cause haemorrhagic disease of the newborn infant, a condition that may present within 2–3 days of birth.

Trace Metals and Metal

Inorganic micronutrients, or trace metals, are essential for normal health and, by definition, make up less

than 0.01 per cent of the body's dry weight.

- **Zinc**

Zinc is a cofactor for certain enzymes, for example polymerases, carbonic dehydratase and alkaline phosphatase. Zinc deficiency may result in a number of clinical states, including growth retardation, alopecia, dermatitis, diarrhoea, poor wound healing, infertility and increased risk of infections. The plasma zinc-carrying protein metallothionine may also prove useful. Note that plasma zinc levels may be low during an acute-phase response, as the zinc is also partly bound to albumin, which is a negative acute-phase reactant. Zinc toxicity is rare, usually occurring after inappropriate administration, and may result in pulmonary oedema, jaundice and oliguria as well as hypocupremia (low plasma copper).

- **Copper**

Copper functions as an enzyme cofactor, for example for cytochromes.

Copper deficiency may cause cardiac arrhythmias, neutropenia, hypochromic anaemia and, in children, bony problems such as subperiosteal haematoma.

Menke's disease is an inborn error of copper transport resulting in low plasma copper concentrations and abnormal hair that has a characteristic 'kink' appearance. Copper is carried on the protein caeruloplasmin, the level of which may be increased due to an acute-phase response, estrogens or pregnancy.

Copper excess can lead to toxicity, causing renal problems, fits, haemolysis and hypotension. Wilson's disease, in which copper excess and decreased caeruloplasmin occur, is an inborn error of metabolism. Wilson's disease Some plasma copper is loosely bound to albumin, but most is incorporated in the protein caeruloplasmin. Copper is mainly excreted in bile.

- **Selenium**

The main function of selenium is to mediate the activity of the enzyme glutathione peroxidase, which acts as an antioxidant.

Deficiency can be caused by poor intake and is most commonly seen in certain areas of China. Patients on artificial nutrition, for example parenteral support, are also more susceptible. Selenium deficiency may also cause cardiomyopathy (Keshan's disease), osteoarthropathy (Kaschin–Beck disease). Selenium may slow the progression of mild Graves' orbitopathy.

- **Manganese**

This is an enzyme cofactor, for example of superoxide dismutase.

Deficiency is associated with vitamin K deficiency and may be seen in patients who are being fed artificially. Manganese excess can occur, for example in miners of manganese ores, and can result in Parkinson-like disease and defects of the basal ganglia. Manganese is mainly biliary excreted, and therefore toxicity may occur with hepatic dysfunction or cholestasis.

- **Chromium**

Chromium is an insulin cofactor. Chromium deficiency can occur on long-term parenteral nutrition, leading to glucose intolerance and neuropathy. Toxicity is associated with gastrointestinal problems, lung cancer and hepatitis.

Metal Poisoning

It would be highly unusual to have a deficiency of the following metals.

- **Mercury**

Mercury poisoning can occur from organic or inorganic salts or elemental mercury vapour. Acute toxicity may result in a metallic taste and respiratory distress, nausea and vomiting. More chronic features include neuropathy and renal dysfunction.

Acute toxicity can be treated with dimercaprol chelating agents, which increase excretion via urine and bile. In chronic exposure, *N*-acetyl penicillamine has been used to chelate mercury.

- **Aluminium**

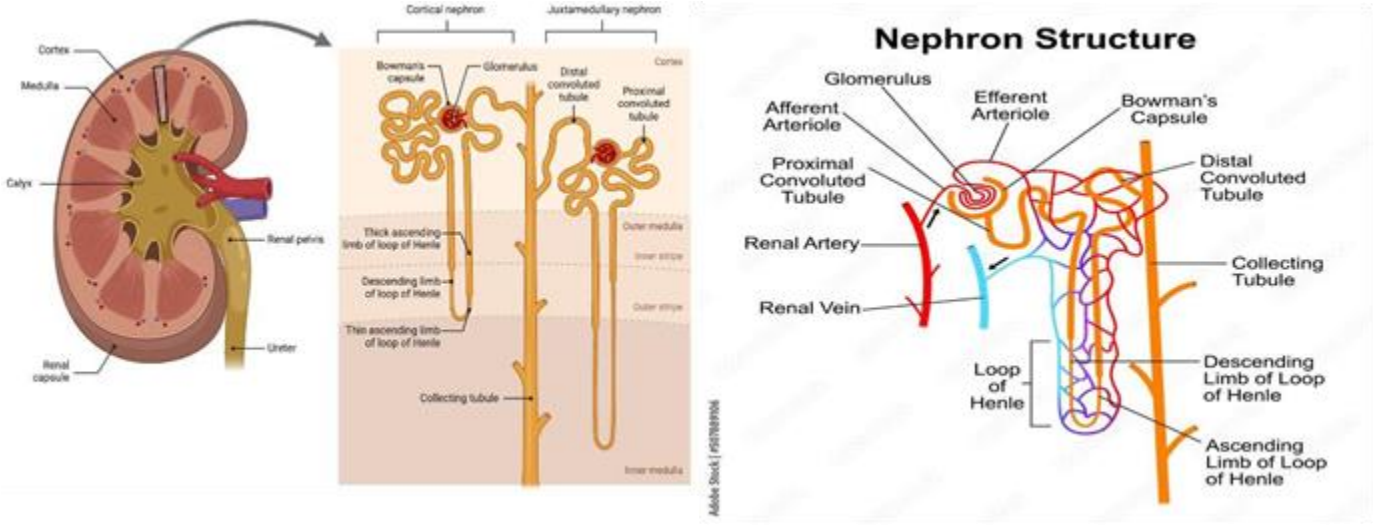
Aluminium toxicity, although rare, is well described in patients with renal impairment. Contamination of the water used in dialysis fluid has been implicated in renal osteodystrophy and dialysis dementia. Toxicity has also been seen in individuals with excess oral intake, such as of aluminium-containing antacids for dyspepsia. Contamination from plastic tubing and glass vials may occur in some long-term total parenteral nutrition patients. Aluminium exposure is diagnosed by plasma aluminium measurements. Desferoxamine has been used to chelate aluminium in toxicity.

- **Lead**

Lead poisoning inhibits several of the enzymes involved in haem synthesis, including PBG synthase and ferrochelatase, and eventually causes anaemia. The urine contains increased amounts of ALA (an early and sensitive test), and coproporphyrin. Some of the symptoms of lead poisoning, such as abdominal pain and peripheral neuropathy, are similar to those of the acute porphyric attack, and may cause difficulty in diagnosis. However, the excretion of PBG is not usually increased. Zinc protoporphyrin concentration rises with increased lead exposure, although the method of choice for assessing exposure to inorganic lead is blood lead concentration. Other features of lead poisoning include lead staining of the teeth and basophilic stippling of red blood cells.

Renal Disorder

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, are invaginated and surround 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 ultrafiltrate 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 contacts 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 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 either glomerular 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 low glomerular 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 (GFR) with Normal Tubular Function

The biochemical findings from the affected nephrons are as follows:

1. Plasma findings

- Elevated urea and creatinine concentrations, indicating uraemia.
- Reduced bicarbonate concentration with decreased blood pH, resulting in metabolic acidosis.
- Increased serum potassium concentration (hyperkalaemia).
- Elevated uric acid and phosphate levels (hyperuricaemia and hyperphosphataemia).

2. Urine findings

- Reduced urine output (oliguria).
- Low sodium concentration, which is appropriate when renal blood flow is reduced and aldosterone secretion is stimulated.
- High urea concentration with increased urine osmolality, which is appropriate when antidiuretic hormone (ADH) secretion is stimulated.

Reduced Tubular Function with Normal Glomerular Filtration Rate

The venous plasma and urine findings reflect tubular dysfunction while glomerular function remains intact.

1. Plasma findings

- Normal urea and creatinine concentrations, indicating preserved glomerular filtration.
- Due to proximal or distal tubular dysfunction:
    - Reduced bicarbonate concentration and low pH (metabolic acidosis).
    - Decreased serum potassium concentration (hypokalaemia).

- Due to proximal tubular dysfunction specifically:
    - Reduced phosphate, magnesium, and uric acid levels (hypophosphataemia, hypomagnesaemia, and hypouricaemia).

2. Urine findings

- Due to proximal and/or distal tubular dysfunction:
    - Increased urine volume.
    - Inappropriately high urine pH relative to plasma pH.
- Due to proximal tubular dysfunction specifically:
    - Generalized aminoaciduria.
    - 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), or reduced intake.

- reduced pressure as a result of the vascular dilatation caused by ‘shock’, causes of which include myocardial infarction, 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, urate or calcium. Obstruction caused by casts and oedema of tubular cells is usually the result of true renal damage.

- Extrarenal obstruction, due to calculi, neoplasms, for example prostate or cervix, urethral strictures or prostatic hypertrophy, any of which may cause sudden obstruction. The finding of a palpable bladder indicates urethral obstruction, and in males is most likely to be due to prostatic hypertrophy, although there are other, rarer, causes.

Early correction of outflow obstruction may rapidly increase the urine output. The longer it remains untreated, the greater the danger of ischaemic or pressure damage to renal tissue. Imaging studies such as renal tract ultrasound may be useful to confirm postrenal obstruction.

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).

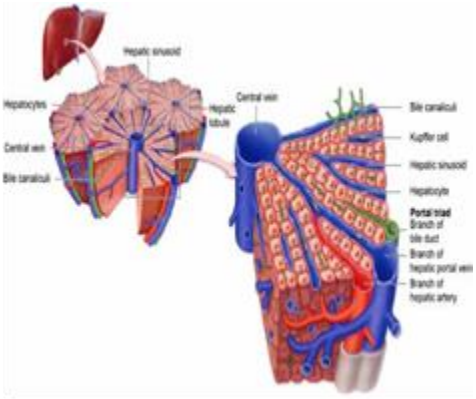
Liver Disorders and Gallstones

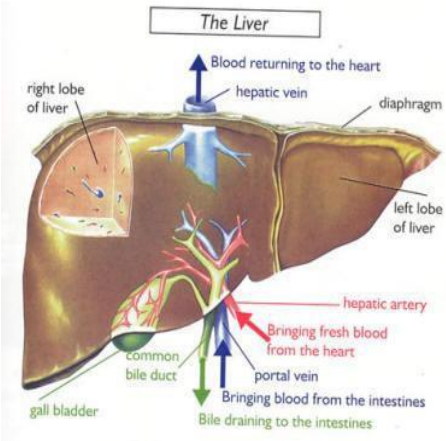
Two main liver lobes are each made up of thousands of lobules. The liver plays a fundamental role in:

- It has a central position in carbohydrate and fat metabolism.
- Storing glycogen at times of glucose repletion and converting excess carbohydrate to fat that it exports as VLDL.
- It is responsible for the synthesis of albumin and many other plasma proteins, as well as most of the coagulation factors.
- It synthesizes bile acids, major constituents of bile.
- Key organ for detoxification, metabolism and inactivation of drugs.
- Metabolism and excretion of many endogenous compounds, including cholesterol, amino acids, steroid and other hormones.
- In this regard it also protects the body against potential carcinogens.

Structure of the Liver

Only about 80% of the cells in the liver are hepatocytes. The functional unit of each liver acinus consists of the portal tract, surrounded by radiating cords of hepatocytes. Blood enters the acinus via the portal tract and passes along the sinusoids towards the central vein. 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.





Hepatic Protein Synthesis

The measurement of certain plasma proteins provides an index of the liver's ability to synthesize protein.

- **Albumin**

In chronic hepatocellular damage, there is impaired albumin synthesis with an accompanying fall in serum albumin. Albumin measurements provide a fairly good index of the progress of chronic liver disease. In acute liver disease, however, there may be little or no reduction in serum albumin, as the biological half-life is about 20 days and the fractional clearance rate is therefore low. Factors other than impaired hepatic synthesis may lead to a decreased serum albumin concentration. These include loss of albumin, ascites, increased degradation, poor nutritional status and a fall as part of the acute-phase response. This often develops when serum albumin falls below 30 g/L.

- **Coagulation Factors**

In liver disease, the synthesis of prothrombin and other clotting factors is diminished, leading to an increased PT. This may be one of the earliest abnormalities seen in patients with hepatocellular damage, because prothrombin has a short half-life (<6 h). Deficiency of fat-soluble vitamin K, due to failure of absorption of lipids, may also cause a prolonged PT. In vitamin K deficiency, the coagulation defect can often be corrected by parenteral administration of vitamin K, but this has no effect in patients with hepatocellular damage.

Bilirubin Production and Metabolism

- **Production:**

The body usually produces about 300 mg of bilirubin per day as a breakdown product of haem. About 80% arises from red cells, and from other haem proteins such as myoglobin and the cytochromes. Iron is removed from the haem molecule, and the porphyrin ring is opened to form bilirubin.

- **Transport in plasma and hepatic uptake**

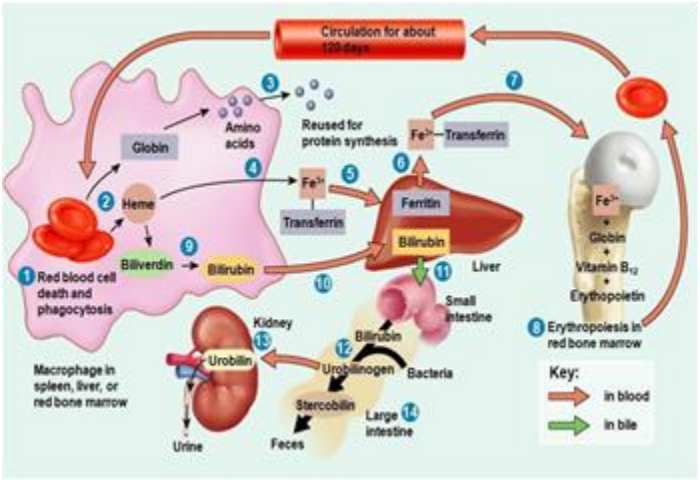
Bilirubin is insoluble in water and is carried in plasma bound to albumin, and is thus not filtered at the glomerulus unless there is glomerular proteinuria. On reaching the liver, the bilirubin taken into the hepatocyte by a specific carrier mechanism.

- **Conjugation of bilirubin and secretion into bile**

In the endoplasmic reticulum of the hepatocyte, the enzyme bilirubin UDP-glucuronyltransferase conjugates bilirubin with glucuronic acid which are water soluble and readily transported into bile.

- **Further metabolism of bilirubin in the gut**

Bilirubin glucuronides cannot be reabsorbed from the gut and are degraded by bacterial action, mainly in the colon, to a mixture of colourless, water-soluble compounds collectively termed urobilinogen. These compounds oxidise to brown compounds known as urobilin and stercobilin and are excreted in the faeces.



The place of biochemical tests in the diagnosis of liver disease

- **The jaundiced patient**

Jaundice is due to hyperbilirubinaemia and becomes clinically apparent when the serum bilirubin exceeds about 50 μmol/L, although smaller degrees of hyperbilirubinaemia may be of diagnostic significance.

- **Pre-hepatic hyperbilirubinaemia**

This is due to overproduction of bilirubin causing an increase in serum unconjugated bilirubin. It occurs in

• haemolytic anaemia.

• haemolytic disease of the newborn, due to rhesus incompatibility.

• ineffective erythropoiesis (e.g. pernicious anaemia).

• gastrointestinal bleeding.

• extensive tissue bruising.

- **Hepatocellular hyperbilirubinaemia**

This can arise from:

1- hepatocellular damage caused by infective agents, drugs/toxins, autoimmune and inherited disorders.

2- cirrhosis usually as a relatively late complication.

3- low activity of bilirubin UDP-glucuronyltransferase in congenital deficiency (Gilbert's syndrome and Crigler–Najjar syndrome).

- **Extrahepatic cholestasis is most often due to**

• gallstones;

• carcinoma of the head of the pancreas.

Liver Function Tests

Most laboratories perform a standard group of tests, which do not assess genuine liver function but are useful for:

1- Detecting the presence of liver disease.

2- Placing the liver disease in the appropriate broad diagnostic category. This then allows the selection of further, more expensive and time-consuming investigations such as ultrasound, CT scanning, magnetic resonance spectroscopy, endoscopy and liver biopsy.

3- Following the progress of liver disease.

Standard group of tests	Property being assessed
Serum albumin, PT	Protein synthesis
Serum bilirubin (total)	Hepatic anion transport
Serum enzyme activities:	
ALT, AST	Hepatocellular integrity
ALP, GGT	Presence of cholestasis

Hepatocytes in the periportal area receive relatively well-oxygenated blood, whereas the hepatocytes surrounding the central vein receive blood that has lost much of its oxygen and exchanged other substances with the cells of the periportal area. The cells surrounding the central vein are therefore the most susceptible to anoxia and injury by a wide range of toxic substances. Hepatocytes in the periportal area also have relatively high concentrations of the enzymes usually measured in blood for diagnostic purposes (e.g. ALP and the aminotransferases ALT and AST), while those surrounding the central vein are relatively deficient in these enzymes. This may help to explain why some patients with centrilobular liver damage may have normal liver enzyme activities.

Hepatocellular damage: Aminotransferase measurements (alanine aminotransferase& aspartate aminotransferase)

The measurement of the activity of ALT or AST in serum provides a sensitive index of hepatocellular damage. Serum ALT measurements are more liver specific than those of AST. In chronic hepatocellular disease (e.g. cirrhosis), serum AST tends to be increased to a greater extent than ALT. The aminotransferases are mainly located in the periportal hepatocytes, and they do not give a reliable indication of centrilobular liver damage. As with all tests based on the release of enzymes from damaged tissue, there is a lag period of some 24 h from the initiation of tissue damage to the first appearance of increased enzyme levels in the plasma.

Cholestasis: alkaline phosphatase and γ-glutamyl transferase

Some enzymes, such as ALP and GGT, are normally attached, or ‘anchored’, to the biliary canalicular and sinusoidal membranes of the hepatocyte. For this reason, ALP and GGT tend to be released into plasma in only small amounts following hepatocellular damage. However, they are released in much greater amounts when there is cholestasis, due, at least in part, to the presence of high hepatic concentrations of bile acids.

Changes in the activities of GGT and ALP often parallel each other in cholestatic liver disease. Serum GGT has the advantage of being more liver specific, as serum ALP may also be increased due to release from bone in bone disease. However, alcohol and many drugs such as anti-convulsant may induce the expression of GGT without causing cholestasis. An isolated increase in GGT should thus be interpreted with caution.

Acute Hepatitis

This is usually caused by viruses (hepatitis A, B, C, D and E, cytomegalovirus or Epstein–Barr). Toxins such as ethanol and paracetamol can also damage the liver. There are often increases in ALT and AST activities and in urobilinogen in urine occur. By the time clinical jaundice appears, serum ALT and AST activities are usually more than six times, and occasionally more than 100 times, the upper reference value. The stools may be very pale, due to impaired biliary excretion of bilirubin, and urobilinogen then disappears more or less completely from the urine. ALP activity is usually in which there is a marked cholestatic element, as occurs in acute alcoholic hepatitis.

Chronic Hepatitis

Hepatic inflammation that persists for more than 6 months is regarded as 'chronic hepatitis'. It may be due to chronic infection with hepatitis virus, alcohol abuse or be autoimmune in origin. Often such patients have an isolated elevation in serum aminotransferase or GGT, unless the disease has progressed to cirrhosis.

Poisoning and Drugs

The most commonly implicated agents in liver dysfunction include paracetamol nonsteroidal anti-inflammatory agents (NSAIDs), statins and antimicrobials, and the mechanisms involved are diverse. Importantly, some agents (e.g. phenytoin, ethanol) can induce GGT synthesis without necessarily causing liver damage.

Cirrhosis of the Liver

Alcoholism, viral hepatitis, autoimmune disease and prolonged cholestasis are the most frequent known causes of cirrhosis in the UK, although in half the cases no obvious cause is found.

Copper in Liver Disease

The liver is the principal organ involved in copper metabolism. The amount it contains is maintained at normal levels by excretion of copper in bile and by incorporation into caeruloplasmin.

Wilson's disease is a rare, hereditary, autosomal recessive disorder with a prevalence of about 1 in 30 000,

Cholestatic Liver Disease

Both extrahepatic (e.g. gallstones) and intrahepatic (e.g. tumours, certain drugs) causes of obstruction cause cholestasis. The distinction between the two is often clinically important from the point of view of further investigation and treatment, but it can rarely be made by biochemical testing. Serum bilirubin is often greatly increased, and there is marked bilirubinuria; urobilinogen often becomes undetectable in urine. Serum ALP and GGT activities are considerably increased, often to more than three times the upper reference values, but serum ALT and AST activities are usually only moderately raised.

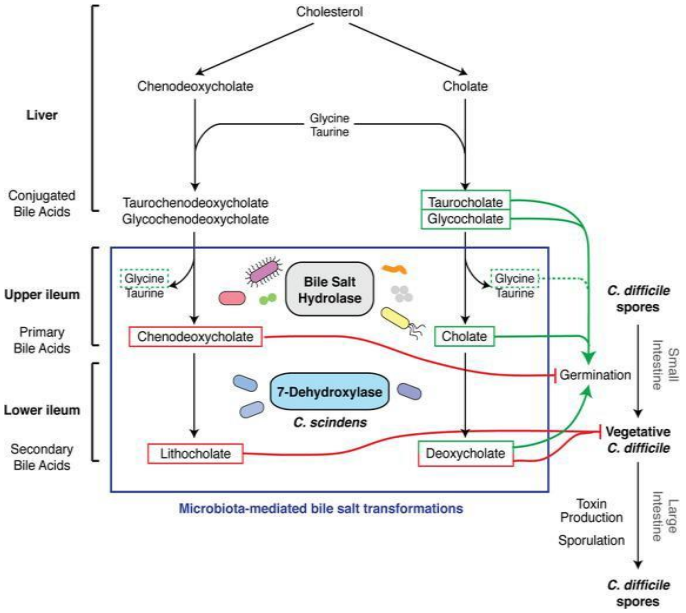
Serum ALP and GGT activities may be markedly increased in patients with partial biliary obstruction, due to local obstruction in one of the smaller biliary ducts, such as often occurs in both primary and secondary carcinoma of the liver. Partial biliary obstruction may have little or no effect on the capacity of the liver to excrete bilirubin, so there may be no evidence of jaundice in these patients, at least initially; bilirubin excretion in the other parts of the liver may be capable of fully compensating for the sector affected by the local biliary obstruction. Biochemical features that may help to distinguish cholestasis from hepatocellular damage.

Bile and Gallstones

Bile acids and bile salts Four bile acids are produced in humans. Two of these, cholic acid and chenodeoxycholic acid, are synthesized in the liver from cholesterol and are called primary bile acids. They are secreted in bile as sodium salts, conjugated with the amino acid glycine or taurine (primary bile salts). These are converted by bacteria within the intestinal lumen to the secondary bile salts, deoxycholate and lithocholate, respectively.

Secondary bile salts are partly absorbed from the terminal ileum and colon and are re-excreted by the liver (enterohepatic circulation of bile salts). Therefore, bile contains a mixture of primary and secondary bile salts.

Deficiency of bile salts in the intestinal lumen leads to impaired micelle formation and malabsorption of fat. Such deficiency may be caused by cholestatic liver disease (failure of bile salts to reach the intestinal lumen) or by ileal resection or disease (failure of reabsorption causing a reduced bile salt pool).



Formation of Bile

Between 1 L and 2 L of bile is produced daily by the liver. This hepatic bile contains bilirubin, bile salts, phospholipids and cholesterol, as well as electrolytes in concentrations similar to those in plasma. Small amounts of protein are also present.

In the gall bladder there is active reabsorption of sodium, chloride and bicarbonate, together with an isosmotic amount of water. Consequently, gall bladder bile is 10 times more concentrated than hepatic bile; sodium is the major cation and bile salts the major anions. The concentrations of other non-absorbable molecules, such as conjugated bilirubin, cholesterol and phospholipids, also increase.

Gallstones

Although most gallstones contain all biliary constituents, they consist predominantly of one. Only about 10 % contain enough calcium to be radio-opaque and in this way, they differ from renal calculi. They can be shown on gall bladder ultrasound. Pigment stones are found in such chronic haemolytic states as hereditary spherocytosis. Increased breakdown of haemoglobin increases bilirubin formation and therefore biliary secretion. The stones consist mostly of bile pigments, with variable amounts of calcium. They are small, hard and dark green or black, and are usually multiple. Rarely, they contain enough calcium to be radio- opaque.

Cholesterol Gallstones

Cholesterol is most likely to precipitate if bile is supersaturated with it; further precipitation on a nucleus of crystals causes progressive enlargement. Not all patients with a high biliary cholesterol concentration suffer from bile stones. Changes in the relative concentrations of different bile salts may favour precipitation. The

stones may be single or multiple. They are described as mulberry-like and are either white or yellowish; the cut surface appears crystalline.

There is no clear association between hypercholesterolemia and the formation of cholesterol gallstones, although both may be more common in obese individuals. However, there may be an increased incidence in patients taking some lipid-lowering drugs, such as the fibric acid derivatives.

Mixed Stones

Most gallstones contain a mixture of bile constituents, usually with a cholesterol nucleus as a starting point. They are multiple-faceted, dark-brown stones with a hard shell and a softer centre and may contain enough calcium to be radio-opaque.

Consequences of Gallstones

Gallstones may remain silent for an indefinite length of time and be discovered only at laparotomy for an unrelated condition. They may, however, lead to various clinical consequences.

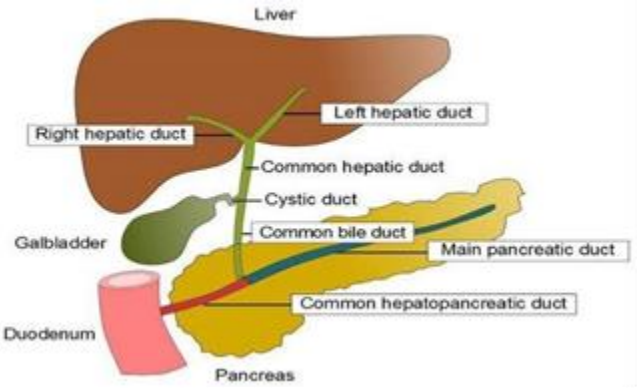
- Biliary colic.

- Acute cholecystitis: obstruction of the cystic duct by a gallstone causes chemical irritation of the gall bladder mucosa by trapped bile and secondary bacterial infection.

- Chronic cholecystitis may also be associated with gallstones.

- Obstruction of the common bile duct occurs if a stone lodges in it. The patient may present with biliary colic, obstructive jaundice. which is usually intermittent, or acute pancreatitis if the pancreatic duct is also occluded.

- Rarely, gallstones may be associated with gallstone ileus or carcinoma of the gall bladder.

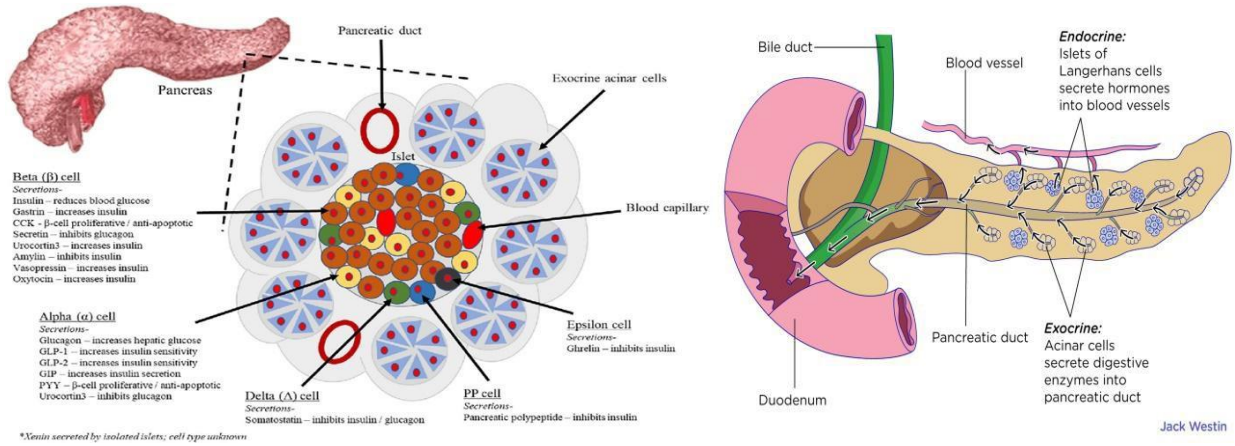


Pancreatic Disorders

Normal Pancreatic Function

Pancreatic secretions can be divided into endocrine and exocrine components. The endocrine function and insulin and glucagon that control the plasma glucose concentration. The exocrine secretions are made up of two components, the alkaline pancreatic fluid and the digestive enzymes. The alkaline fluid is primarily responsible for neutralizing gastric acid secretions, thus providing an optimal environment for duodenal digestive enzyme activity.

These enzymes include the proteases trypsin, elastase, chymotrypsin, amylase and lipase. Gut peptides control pancreatic secretion and are released from the duodenum in response to a rise in the hydrogen ion concentration or to the presence of food. They include secretin (which stimulates the release of a high volume of alkaline fluid) and cholecystokinin (which stimulates the release of a fluid rich in enzymes).



Insulin

Insulin is the most important hormone controlling plasma glucose concentrations. A plasma glucose concentration of greater than about 5 mmol/L acting via the glucose transporter 2 stimulates insulin release from the pancreas b-cell. These cells produce proinsulin, which consists of the 51-amino-acid polypeptide insulin and a linking peptide (C-peptide). Splitting of the peptide bonds by prohormone convertases releases via intermediates (mostly 32–33 split proinsulin) equimolar amounts of insulin and C-peptide into the ECF.

Insulin binds to specific cell surface receptors on muscle and adipose tissue, thus enhancing the rate of glucose entry into these cells. Insulin-induced activation of enzymes stimulates glucose incorporation into glycogen (glycogenesis) in liver and muscle. Insulin also inhibits the

production of glucose (gluconeogenesis) from fats and amino acids, partly by inhibiting fat and protein breakdown (lipolysis and proteolysis).

The transport of glucose into liver cells is insulin independent but, by reducing the intracellular glucose concentration, insulin does indirectly promote the passive diffusion of glucose into them. Insulin also directly increases the transport of amino acids, potassium and phosphate into cells, especially muscle; these processes are independent of glucose transport. In the longer term, insulin regulates growth and development and the expression of certain genes.

Glucagon

Glucagon is a single-chain polypeptide synthesized by the a-cells of the pancreatic islets. Its secretion is stimulated by hypoglycaemia. Glucagon enhances hepatic glycogenolysis (glycogen breakdown) and gluconeogenesis.

Somatostatin

This peptide hormone is released from the D cells of the pancreas and inhibits insulin and growth hormone release.

Exocrine Pancreatic Function Plasma Enzymes

Plasma enzyme measurements are of limited value in assessing exocrine function. They include the following.

Amylase

This enzyme consists of two forms, one of salivary gland origin and one of pancreatic origin. In acute pancreatitis, total plasma amylase activity is usually significantly increased due to release from damaged cells. Typically, plasma amylase activity increases about five-fold in acute pancreatitis, but plasma enzyme activities of up to, and even above, this value may be reached in a number of other disorders, in particular after intestinal perforation and renal failure. Occasionally, the plasma enzyme activity in acute pancreatitis may not be very high and usually falls rapidly as the enzyme is excreted in the urine. Consequently, a high plasma amylase activity is only a rough guide to the presence of acute pancreatitis, and normal or only slightly raised values do not exclude the diagnosis. Plasma amylase concentrations can be spuriously low or normal in acute pancreatitis evoked by severe hypertriglyceridaemia. In such circumstances a raised urinary amylase concentration may facilitate diagnosis or clearing the plasma lipaemia by centrifugation prior to assay. Haemorrhagic pancreatitis or chronic pancreatitis can also show a normal plasma amylase concentration.

Lipase

This enzyme is more specific for the pancreas and can be useful to measure if the source of a raised plasma amylase concentration is not obvious. Lipase has a longer half-life than amylase and thus may be useful in the late diagnosis of acute pancreatitis, when amylase activity can fall within the reference range.

Trypsin

This may be used to screen for cystic fibrosis during the first 6 weeks of life. Blockage of pancreatic ductules by sticky mucous secretion causes high plasma trypsin concentrations. After about 6 weeks, plasma concentrations may fall as pancreatic insufficiency develops; normal levels do not exclude the diagnosis.

Duodenal enzymes

Measurement of pancreatic enzymes and the bicarbonate concentration in duodenal aspirates before and after stimulation with cholecystokinin and secretin is not very suitable for routine use because of the difficulty in positioning the duodenal tube and in quantitative sampling of the secretions. ‘Tubeless tests’ have been developed that avoid the need for intubation and that overcome the difficulties of invasive sample collection.

Acute pancreatitis

Acute pancreatitis due to the necrosis of pancreatic cells is associated with the release of enzymes into the retroperitoneal space and bloodstream. The presence of pancreatic juice in the peritoneal cavity causes severe abdominal pain and shock. A vicious circle is set up as the released enzymes digest more pancreatic cells. Acute pancreatitis may be idiopathic, but may follow gallstones, obstruction of the pancreatic duct or regurgitation of bile along this duct.

Other predisposing factors include excess alcohol ingestion and trauma to the pancreas. Hypercalcaemia and hypertriglyceridaemia may also evoke acute pancreatitis, as can certain drugs such as opiates.

Carcinoma of the pancreas

This tends to present late. Lesions at the head of the organ may cause obstructive jaundice; extensive gland destruction may cause late-onset diabetes mellitus. The concentration of the tumour marker CA19–9 may be raised in pancreatic carcinoma.

Disorders of Lipid Metabolism

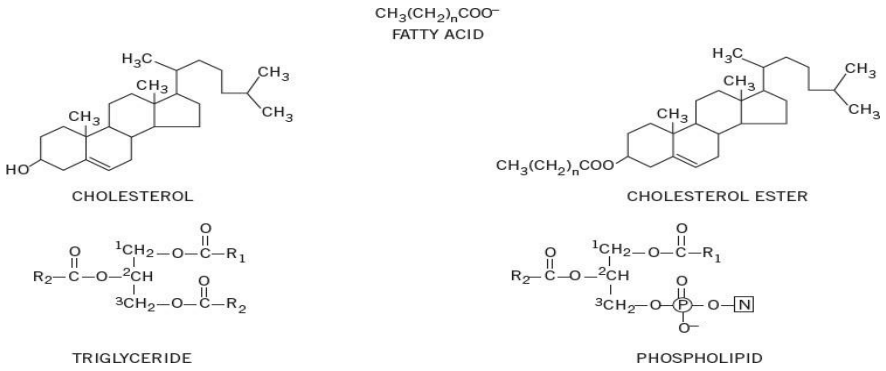
Disorders of Lipid Metabolism

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 disorders associated 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.

Triglyceride

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 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. Lipids can be derived from food (exogenous) or synthesized in

the body (endogenous). The water-soluble (polar) groups of proteins, phospholipids and free cholesterol face outwards and surround an inner insoluble (nonpolar) core of triglyceride and cholesterol esters.

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.

Class of Lipoprotein	Density	Electrophoretic Mobility	%Composition Lipid	Protein	Major lipid Present
Chylomicrons	< 0.96	Origin	98 %	2 %	Mainly Triglycerides
VLDL	0.96-1.006	Pre-β region	91	9	Mainly Triglycerides
LDL	1.006-1.063	β region	79	21	Mainly Cholesterol
HDL	1.063-1.21	α region	50	50	Mainly Cholesterol & Phospholipids

Lipoprotein Turnover:

1. Chylomicrons

Initially nascent chylomicrons are assembled in the intestine from triacylglycerols, phospholipids, cholesterol, apo A and apo B-48. They are transported to blood via lymphatics. In the blood, apo C and apo E are added to these chylomicrons from HDL to form complete chylomicrons.

In extrahepatic tissue capillaries, lipoprotein lipase hydrolyzes TAG to glycerol and free fatty acids. The free fatty acids are esterified back to triacylglycerols and stored by adipose tissue. Glycerol is taken up by the liver. Chylomicrons, after losing triacylglycerols, lose apo A and apo C also to form chylomicron remnants. Apo A and apo C return to HDL. Apo E is retained. Chylomicron remnants are taken up by liver by receptor mediated endocytosis, mediated by apo E.

2. VLDL

Liver synthesizes nascent VLDL consisting of triacylglycerols, phospholipids, cholesterol esters, cholesterol, apo B-100, apo C and apo E. It becomes complete VLDL in the blood after addition of extra apo C and apo E from HDL.

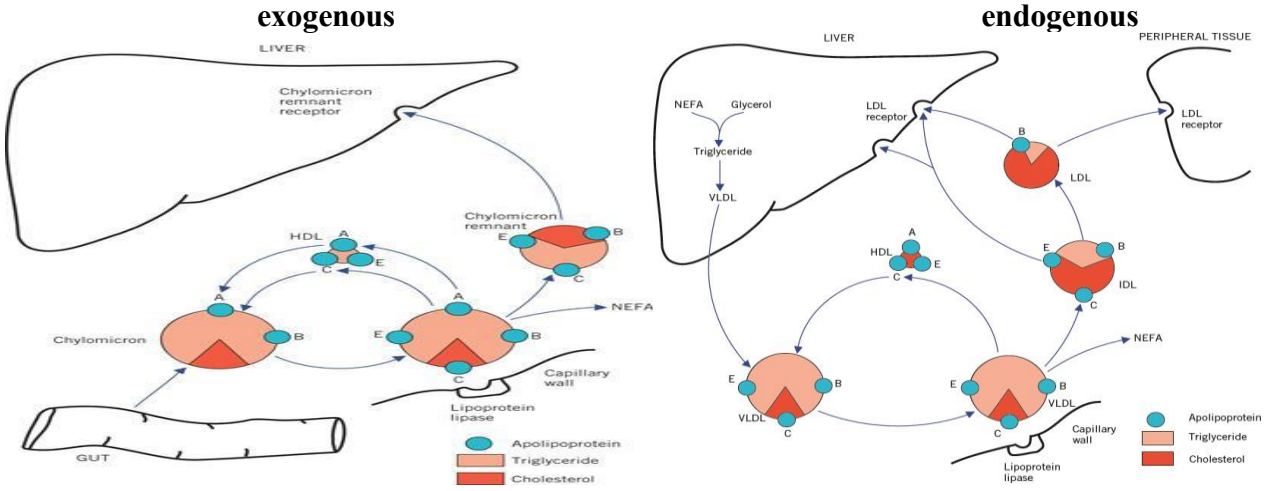
Lipoprotein lipase hydrolyzed triacylglycerols of VLDL to release fatty acids. Then it loses its apo C (which is returned to HDL) and becomes VLDL remnant (also called as the intermediate density lipoprotein IDL). IDL is either taken up by liver or loses its apo E to become LDL.

3. LDL

It is obtained from VLDL. It consists of triacylglycerols, phospholipids, cholesterol and its esters and apo B-100. About half of the circulating LDL is taken up by extrahepatic tissues (which have Apo B- 100 specific LDL receptor) and degraded in these tissues to release cholesterol. Thus, LDL transports the cholesterol to the extrahepatic tissues. The remaining LDL is degraded in liver.

4. HDL

It is synthesized and secreted by liver and intestine. The nascent HDL is discoid in shape and its core is almost empty. LCAT (Lecithin cholesterol acyl transferase) enzyme bound with HDL converts phospholipid and free cholesterol to form cholesterol ester and lysolecithin. The cholesterol ester is then transferred to the core of nascent HDL. As more and more cholesterol ester enters to the core of nascent HDL, it becomes spherical in shape to form mature HDL. HDL consists of triacylglycerols, phospholipids, cholesterol and its esters, apo A, apo C and apo E. It serves as reservoir of apo C and apo E for formation of chylomicrons and VLDL. HDL is finally taken by liver and releases the cholesterol. HDL transports the cholesterol from extrahepatic tissues to liver.



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.

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 decreases in the blood.

b) Abetalipoprotenemia:

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.

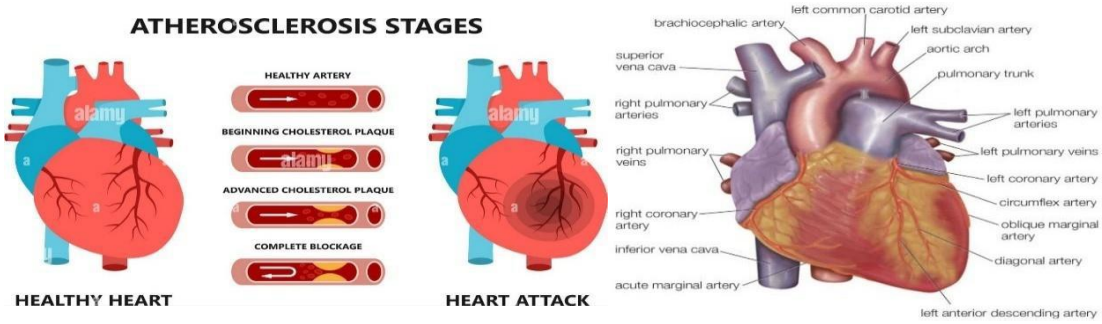
Cholesterol

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

Hypercholesterolemia and development of atherosclerosis and Chronic Heart Disease (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 chronic heart disease CHD):

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

• Obstructive jaundice: Cholesterol is mainly excreted through bile. Tn obstructive jaundice, there is an obstruction in the cholesterol excretion through bile, causing hypercholesterolemia.

• Hypothyroidism: Thyroid hormones play a role in reducing serum cholesterol level. So, cholesterol level increases in hypothyroidism.

• Nephrotic syndrome: in nephrotic syndrome, lipoprotein lipase (which is required to clear lipids from blood) 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.

Fatty liver

Definition: Normally liver cells contain only 5 % of fats. If the fat level increases above 5 % in the liver cells, then the condition is known as fatty liver. Liver has the ability to take up fatty acids from the blood and esterify it to fat. This fat (Triglycerides) along with the endogenously synthesized triglycerides are incorporated into VLDL & transported out of the liver to the extra-hepatic tissues. This is a very finely balanced process. Imbalance in the rate of triacylglycerol synthesis and export causes fatty liver. Excessive accumulation of fat in the liver is pathogenic. It leads to fibrotic changes in the liver causing fibrosis, then cirrhosis and finally hepatic failure.

Fatty liver is seen in two conditions:

1) Increased synthesis of triacylglycerol in liver 2) In the metabolic block of VLDL formation

1. Increased synthesis of triacylglycerol in liver:

Causes: diabetes mellitus, starvation, high fat diet, high calorie intake, alcoholism.

2. In the metabolic block of VLDL formation:

Endogenous triacylglycerols are transported out of liver by VLDL. Any metabolic block in VLDL formation, fat is not properly transported out of the liver, leading to the accumulation of fat in the liver causing fatty liver

Metabolic Syndrome

The characteristic features are abdominal obesity and insulin resistance or decreased glucose tolerance. The body cannot properly use glucose even in presence of normal insulin level. In other words, body cannot use insulin efficiently. Therefore, the metabolic syndrome is also called the insulin resistance syndrome. People with the MetS are at increased risk of coronary heart disease and type 2 diabetes. The MetS has become increasingly common in the developing countries.

Causes for Mets or Associated Conditions Include:

obesity; alcoholism; sedentary lifestyle with lack of physical exercise; polycystic ovarian syndrome (PCOS); hypercortisolism (e.g. steroid use or Cushing's disease); certain drugs and genetic causes such as mutations of the insulin receptors.

Effects of Insulin Resistance:

hydrolysis of stored triglycerides or fats, which elevates free fatty acids (FFA) in the plasma; reduction of glucose uptake or glucose utilization among muscle cells and reduction of

glycogenesis (glycogen formation) or decreasing glucose storage in the liver cells with both effects leading to elevation of blood sugar levels. In obese patients especially those with high visceral fat, compensatory hyperinsulinemia causes the down regulation of the insulin receptors potentiated by the inherent defects within the target cells itself. Both aspects play a role in the development of insulin resistance.

Laboratory Tests for MetS:

The fasting insulin level greater than 60 pmol/L is considered to be positive evidence of insulin resistance. Further, hyperinsulinemic euglycemic clamp test may be done in selected cases; however, this is rarely performed in the clinical setting. But this is considered to be the gold standard because it measures the exact amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia.

Management of the Metabolic Syndrome

i. Weight loss to achieve a desirable weight.

ii. Moderate exercise every day.

iii. Reduced intake of saturated fats, trans fatty acids and cholesterol.

Diabetes Mellitus

Diabetes mellitus is the third leading cause of death (after heart disease and cancer) in many developed countries. It affects about 6 to 8% of the general population. The complications of diabetes affect the eye, kidney and nervous system. Diabetes mellitus is a clinical condition characterized by increased blood glucose level (hyperglycemia) due to insufficient or inefficient (incompetent) insulin on the target tissues. As a consequence, the blood glucose level is elevated which spills over into urine in diabetes mellitus (Greek: diabetes—a siphon or running through; mellitus—sweet).

Sources of Blood Glucose

1. **Dietary sources**: The dietary carbohydrates are digested and absorbed as monosaccharides (glucose, fructose, galactose etc.). The liver is capable of converting fructose and galactose into glucose.

2. Gluconeogenesis: The degradation of glycogen in muscle results in the formation of lactate. Breakdown of fat in adipose tissue will produce free glycerol and propionate. Lactate, glycerol, propionate and some amino acids are good precursors for glucose synthesis (gluconeogenesis) that actively occurs in liver and kidney. Gluconeogenesis continuously adds glucose to the blood. Cori cycle is responsible for the conversion of muscle lactate to glucose in liver.

3. Glycogenolysis: Degradation of glycogen in liver produces free glucose. This is in contrast to muscle glycogenolysis where glucose is not formed in sufficient amount due to lack of the enzyme glucose 6-phosphatase. However, the contribution of liver glycogenolysis to blood glucose is rather limited and can meet only the short intervals of emergency. This is due to the limited presence of glycogen in liver. An adult liver (weighing about 1.5 kg) can provide only 40-50 g of blood glucose from glycogen, that can last only for a few hours to meet the body requirements. the sources of blood glucose during a normal day (24 hours) are given. Glucose is primarily derived from glycogenolysis (of hepatic glycogen) between the meals. Gluconeogenesis becomes a predominant source of glucose in late night (after depletion of hepatic glycogen). During day time, gluconeogenesis may be more or less active, depending on the frequency of consumption of snacks, coffee, tea, fruit juices etc.

Utilization of blood glucose

Certain tissues like brain, erythrocytes, renal medulla and bone marrow are exclusively dependent on glucose for their energy needs. When the body is at total rest, about two-thirds of the blood glucose is utilized by the brain. The remaining one-third by RBC and skeletal muscle.

A regular supply of glucose, by whatever means it may be, is absolutely required to keep the brain functionally intact. The different metabolic pathways (glycolysis, glycogenesis, HMP shunt etc.) responsible for the utilization of blood glucose, The synthesis of fat from acetyl CoA and glycerol. Kidney plays a special role in the homeostasis of blood glucose. Glucose is continuously filtered by the glomeruli, reabsorbed and returned to the blood. If the level of glucose in blood is above 160-180 mg/dl, glucose is excreted in urine (glycosuria). This value (160-180 mg/dl) is referred to as renal threshold for glucose.

Role of Hormones in Blood Glucose Homeostasis

Hormones play a significant role in the regulation of blood glucose concentration, Primarily, insulin lowers blood glucose level (hypoglycemic) while the rest of the hormones oppose the actions of insulin (hyperglycemia) are Glucagon, Epinephrine, Thyroxine, Glucocorticoids, Growth hormone and adrenocorticotropic hormone (ACTH).

Mechanisms of Action of Insulin

1. Insulin Receptors

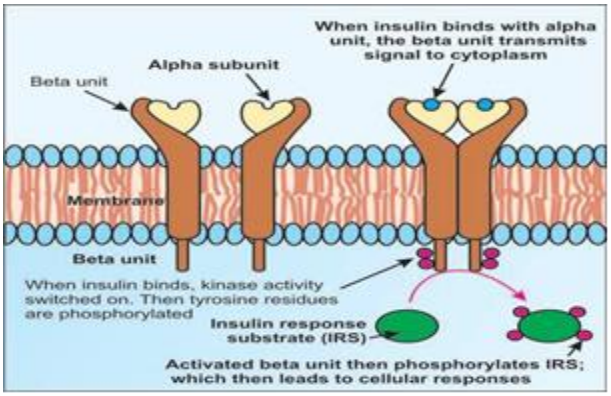
Insulin acts by binding to a plasma membrane receptor on the target cells. In obesity, the number of receptors is decreased and target tissue becomes less sensitive to insulin (diabetes mellitus Type 2). Insulin receptor is a glycoprotein with 4 subunits; 2 alpha and 2 beta subunits. The alpha units are located on the extracellular side,

to which insulin binds. The beta subunits traverse the membrane and are exposed on the cytoplasmic side .Beta subunit has tyrosine kinase activity.

2. Signal Transduction

Insulin binds to the alpha subunit. This binding activates the tyrosine kinase activity of the beta subunit, leading to autophosphorylation of the beta subunit. This event, in turn, phosphorylates insulin receptor substrates (IRS).

Glucose Uptake



Classification of Diabetes Mellitus

1. Type 1 Diabetes Mellitus

(formerly known as Insulin-dependent diabetes mellitus; IDDM). About 5% of total diabetic patients are of type 1. Here circulating insulin level is deficient. It is subclassified as:

a. Immune mediated and b. Idiopathic.

2. Type 2 Diabetes Mellitus

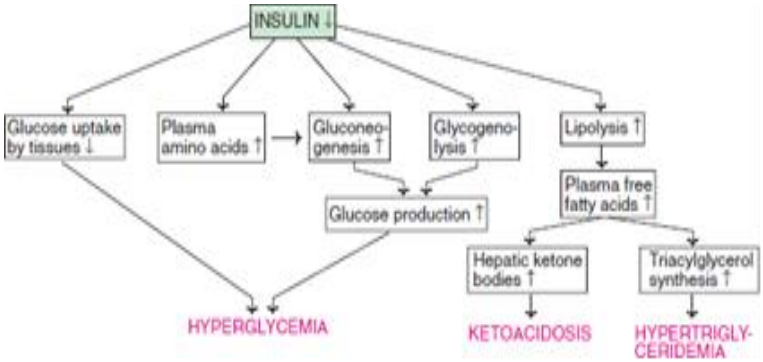
(formerly known as non-insulin dependent diabetes mellitus; NIDDM). Most of the patients belong to this type. Here circulating insulin level is normal or mildly elevated or slightly decreased, depending on the stage of the disease. This type is further classified as: Obese, non-obese, and Maturity onset diabetes of young (MODY).

3. Diabetic prone states: Gestational diabetes mellitus (GDM), Impaired glucose tolerance (IGT), and Impaired fasting glycemia (IFG)

4. Secondary to other known causes: endocrinopathies (Cushing's disease, thyrotoxicosis, acromegaly), drug induced (steroids, beta blockers, etc.), and pancreatic diseases (chronic pancreatitis, fibro calculus pancreatitis, hemochromatosis, cystic fibrosis).

Character	*Insulin-dependent diabetes mellitus (IDDM)*	*Non-insulin dependent diabetes mellitus (NIDDM)*
General		
Prevalence	10-20% of diabetic population	80-90% of diabetic population
Age at onset	Usually childhood (<20 yrs)	Predominantly in adults (>30yrs)
Body weight	Normal or low	Obese
Genetic predisposition	Mild or moderate	Very strong
Biochemical		
Defect	Insulin deficiency due to destruction of β-cells	Impairment in the production of insulin by β-cells and/or resistance of target cells to insulin
Plasma insulin	Decreased or absent	Normal or increased
Auto antibodies	Frequently found	Rare
Ketosis	Very common	Rare
Acute complications	Ketoacidosis	Hyperosmolar coma
Clinical		
Duration of symptoms	Weeks	Months to years
Diabetic complications at diagnosis	Rare	Found in 10-20% cases
Oral hypoglycaemic drugs	Not useful for treatment	Suitable for treatment
Administration of insulin	Always required	Usually not necessary

Diabetes mellitus is associated with several metabolic alterations. Most important among them are hyperglycemia, ketoacidosis and hypertriglyceridemia



1. **Hyperglycemia**: Elevation of blood glucose concentration is the hallmark of uncontrolled diabetes. Hyperglycemia is primarily due to reduced glucose uptake by tissues and its increased production via gluconeogenesis and glycogenolysis. When the blood glucose level goes beyond the renal threshold, glucose is excreted into urine (glycosuria). Glucose toxicity: High concentrations of glucose can be harmful causing osmotic effects/ hypertonic effects (water drawn from cells into extracellular fluid and excreted into urine, resulting in dehydration), β- cell damage by free radicals (due to enhanced oxidative phosphorylation, oxidative stress, and increased free radicals) and glycation of proteins (associated with diabetic complications neuropathy, nephropathy, retinopathy etc.).

2. **Ketoacidosis**: Increased mobilization of fatty acids results in overproduction of ketone bodies which often leads to ketoacidosis.

3. **Hypertriglyceridemia**: Conversion of fatty acids to triacylglycerols and the secretion of VLDL and chylomicrons is comparatively higher in diabetics. Further, the activity of the enzyme lipoprotein lipase is low in diabetic patients. Consequently, the plasma levels of VLDL, chylomicrons and triacylglycerols are increased. Hypercholesterolemia is also frequently seen in diabetics.

Long term effects of diabetes

Hyperglycemia is directly or indirectly associated with several complications. These include atherosclerosis, retinopathy, nephropathy and neuropathy. The biochemical basis of these complications is not clearly understood. It is believed that at least some of them are related to microvascular changes caused by glycation of proteins.

	Normal persons	Criteria for diagnosing diabetes	Criteria for diagnosing IGT
Fasting	**< 110 mg/dl** <(6.1mmol/L)	**> 126 mg/dl** >(7.0 mmol/L)	**110 to** 126 mg/dl
1 hr (peak) after glucose	**< 160 mg/dl** < (9 mmol/L)	Not prescribed	Not prescribed
2 hr after glucose	**< 140 mg/dl** < (7.8 mmol/L)	**> 200 mg/dl** >(11.1 mmol/L)	**140 to** 199 mg/dl

Disorder of protein, Uric acid, gout and purine metabolism

Purine metabolism and uric acid

Purines are simple, cyclic organic molecules that are essential constituents of the nucleic acids, both DNA and RNA. The purine bases adenine and guanine comprise the 'A' and 'G' of the DNA code. When a ribose sugar moiety is linked to the purine base a nucleoside is formed (e.g. adenosine, made up of the purine adenine linked to ribose). The addition of a phosphate group to the ribose ring generates the corresponding nucleotide (e.g. adenosine 5-monophosphate, AMP).

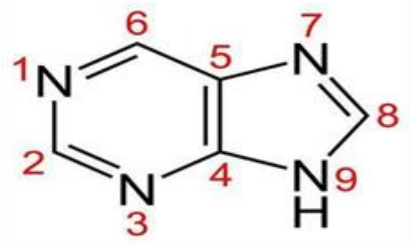
As such the purines are essential constituents of metabolically important compounds such as ATP. Uric acid is the end-product of breakdown of the purine bases. It emphasizes that the source of the purines can be from the three routes of diet, nucleic acid breakdown or de novo purine synthesis. The liver is the main source of urate and, once formed, urate is predominantly excreted via the kidneys.

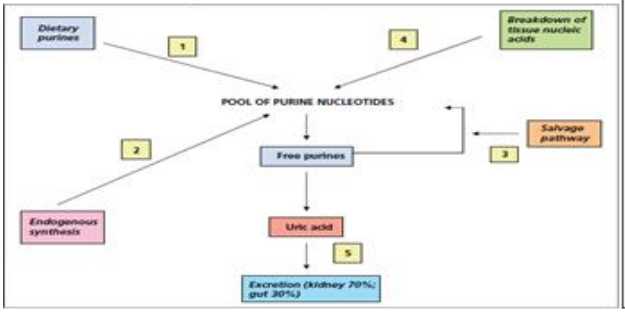
The clinical importance of purines rests largely on the disorder termed gout, an inflammatory arthritis resulting from uric acid deposition in the joints. An increase in serum uric acid (as the anion, urate, at physiological pH) is the strongest risk factor for gout although gout may occur when serum urate levels are within the normal range. In man, urate is the end-product of purine metabolism such that urate accumulation may arise from:

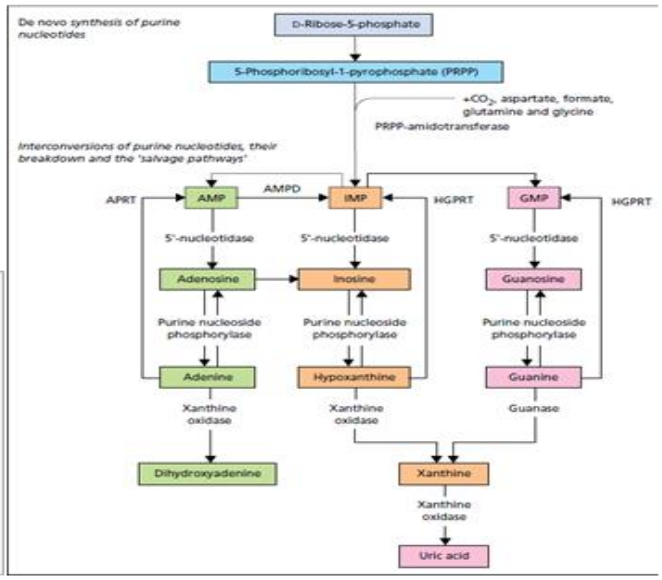
• increased dietary purine intake or dietary factors affecting urate production;

• increased formation (either increased nucleic acid breakdown or increased de novo synthesis of purines);

• decreased renal excretion;







Humans and higher primates lack the enzyme uricase, so uric acid is not converted into the more soluble allantoin.

Primary gout occurs without a clear cause but is commonly linked to obesity, alcohol intake, high blood pressure, and high triglycerides.

Secondary gout develops due to specific causes such as kidney failure, increased cell breakdown, certain drugs, or inherited enzyme defects, and understanding urate metabolism helps explain gout.

Hyperuricaemia

In addition to the deposition of sodium monourate crystals in affected joints uric acid calculi in the kidneys may also form due to hyperuricaemia, and the lower pH values possible in urine can predispose to this problem. As serum urate levels rise, the risk of precipitation of sodium urate increases, although the relationship between the presence and severity of hyperuricaemia and the development of arthritis or renal calculi is more complex than simple considerations of solubility might suggest.

Dietary factors

• **High-purine diets**: A high meat diet or one rich in seafood increases the purine load.
• **Alcohol excess:** Nutritional surveys have established a strong link between hyperuricaemia and alcohol intake.
• **Fructose-containing beverages**.

Endogenous overproduction of urate

A number of mechanisms are possible. For example:

• Unspecified overactivity of the pathways of nucleotide metabolism, as opposed to nucleic acid synthesis, leading to urate formation (‘endogenous overproduction’).

• Decreased activity of the ‘salvage’ pathway so that purine bases are metabolised to urate rather than re-incorporated into nucleotides and nucleic acids.

• Increased nucleic acid breakdown when cell turnover or destruction is increased.

Defective Elimination of Urate

Renal excretion of urate is a complex process. Except for a small fraction bound to plasma proteins, urate is completely filtered at the glomerulus; this is then mostly reabsorbed in the proximal tubule. In the distal tubule, there is both active secretion and post secretory reabsorption at a more distal site. These processes can all be affected by disease or drugs:

• **GFR**: When the GFR becomes reduced for any reason urate retention occurs.

• **Tubular reabsorption**: Around 90% of the filtered urate load is reabsorbed in the proximal nephron via specific anion transporters. The specific transport called URAT1 is a target for drugs such as probenecid that inhibit its activity and increase the excretion of urate.

• **Distal tubular secretion**: Urate excretion also depends upon distal tubular secretion. This process is competed for by other organic acid anions such as lactate and 3-hydroxybutyrate. Any condition that gives rise to lactic acidosis or ketosis tends to be associated with hyperuricaemia.

Gout

Hyperuricaemia is linked to gout, which causes recurrent attacks of painful monoarticular arthritis, commonly affecting the first metatarsophalangeal joint.

Gout usually progresses from an asymptomatic phase to acute attacks and may later become chronic with tophi formation.

Urate deposition can also cause kidney stones, increasing the risk of renal dysfunction, especially with dehydration or low urine pH.

Gout is associated with metabolic syndrome, hypertension, and increased cardiovascular morbidity and mortality.

Although common in older men and post-menopausal women, many people with high serum urate never develop gout, and acute attacks may occur even with normal urate levels.

• **Primary gout**, by definition, occurs in the absence of acquired or monogenetic conditions although there is no doubt that genetic factors contribute, with about 60% of variability in serum urate genetically determined. The present evidence is that differences in urate excretion rates contribute principally to urate levels, overproduction being a less important factor. The association with hyperlipidaemia, ischaemic heart disease and metabolic syndrome may also reflect a familial component, although it is sometimes difficult to disentangle the genetic and environmental factors.

Diagnosis of gout is usually clinical, based on typical joint involvement, previous similar attacks, response to colchicine, and raised serum urate after excluding secondary causes. However, high serum urate supports but does not confirm gout, and up to one-third of patients may have normal levels during an acute attack. Definitive diagnosis requires joint aspiration and identification of needle-shaped, negatively birefringent monosodium urate crystals. Acute gout occurs when urate crystals enter the joint and are taken up by immune cells, triggering inflammation. Interleukin-1β plays a key role, and colder peripheral joints are commonly affected due to reduced urate solubility.

There are rare forms of gout that arise from clearly defined and inherited metabolic enzyme defects which increase uric acid formation. It is convenient to categorise these enzymatic defects as secondary gout to distinguish them from the common primary gout.

• **Secondary gout** describes the condition in association with other disorders that secondarily increase urate formation (e.g. increased cell death in myeloproliferative disorder) or decrease excretion (e.g. renal failure). The group also includes the rare metabolic causes of overproduction.

In practice, both primary and secondary factors may contribute. For example, the patient may have a primary predisposition to hyperuricaemia which is then compounded by alcohol excess.

Hypouricaemia

Low serum urate may arise as follows

• Dilutional states such as SIADH (Syndrome of inappropriate antidiuretic hormone) or pregnancy.

• Decreased production. This can be found in severe liver disease. Another example is the condition called xanthinuria arising from an inherited deficiency of the enzyme xanthine oxidase (which normally converts xanthine to urate). Xanthine crystals can form in the urinary tract.

• Increased excretion. This is usually in association with defective proximal tubular reabsorption (Fanconi syndrome).

• Rasburicase This is a genetically engineered enzyme that is a urate oxidase. It converts uric acid to the water-soluble allantoin. It is especially helpful in preventing the renal and other complications of excessive urate formation in the tumour lysis syndrome (massive cell lysis such as is found during treatment of haematological malignancies). It has a short half-life but can effectively reduce serum urate to very low levels.

Modifications of rasburicase to increase its half-life are starting to find a place in the treatment of gout. A low serum urate has not usually been regarded as pathological in its own right. However, uric acid has anti-oxidant properties that may be more important than have hitherto been realised. For example, there is a literature that reports associations between low serum urate and a variety of neurological disorders such as multiple sclerosis and Parkinson disease. It is speculated that urate may help prevent damage to nervous tissue from oxidants such as peroxynitrite, although it is unclear if the low urate is a causal factor or consequence of the neurological problem.

Disorders of Haem Metabolism: Iron and the Porphyrias

Hemoglobin is a conjugated protein having heme as the prosthetic group and the protein, the globin. It is a tetrameric protein with 4 subunits, each subunit having a prosthetic heme group and the globin polypeptide. The polypeptide chains are usually two alpha and two beta chains. Hemoglobin has a molecular weight of about 67,000 Daltons. Each gram of Hb contains 3.4 mg of iron. Heme is present in

a. Hemoglobin

b. Myoglobin

c. Cytochromes

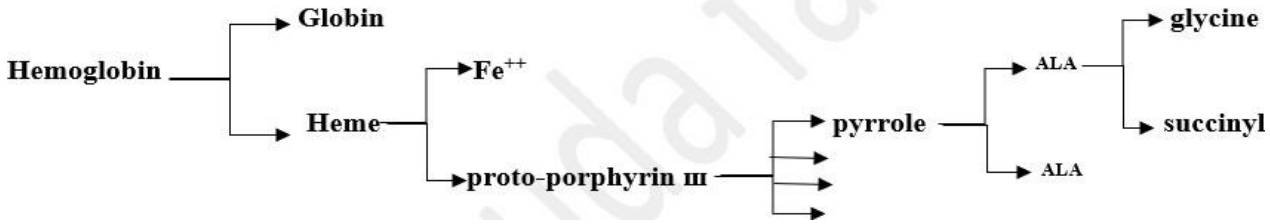
d. Peroxidase

e. Catalase

f. Tryptophan pyrrolase

g. Nitric oxide synthase

Heme is produced by the combination of iron with a porphyrin ring. Chlorophyll, the photosynthetic green pigment in plants is magnesium-porphyrin complex.



Structure of Heme

i. Heme is a derivative of the porphyrin. Porphyrins are cyclic compounds formed by fusion of 4 pyrrole rings linked by methenyl (=CH–) bridges.

ii. Since an atom of iron is present, heme is a ferroprotoporphyrin. The pyrrole rings are named as I, II, III, IV and the bridges as alpha, beta, gamma and delta. The possible areas of substitution are denoted as 1 to 8.

iii. When the substituent groups have a symmetrical arrangement (1,3,5,7 and 2,4,6,8) they are called the I series. The III series have an asymmetrical distribution of substituent groups (1,3,5,8 and 2,4,6,7).

iv. Type III is the most predominant in biological systems. The usual substitutions are:

a. propionyl ($–CH_2–CH_2–COOH$) group

b. acetyl ($–CH_2–COOH$) group

d. vinyl ($–CH=CH_2$) group

Biosynthesis of Heme

Heme can be synthesized by almost all the tissues in the body. Heme is synthesized in the normoblasts, but not in the matured erythrocytes. The pathway is partly cytoplasmic and partly mitochondrial.

Step 1: ALA synthesis

The synthesis starts with the condensation of succinyl CoA and glycine in the presence of pyridoxal phosphate to form delta amino levulinic acid (ALA). Hence anemia may be manifested in pyridoxal deficiency. The enzyme ALA synthase is located in the mitochondria.

Step 2: Formation of PBG

Next few reactions occur in the cytoplasm. Two molecules of ALA are condensed to form porphobilinogen (PBG). The condensation involves removal of 2 molecules of water and the enzyme is ALA dehydratase Porphobilinogen is a monopyrrole. The enzyme contains zinc and is inhibited by lead.

Step 3: Formation of UPG

Condensation of 4 molecules of the PBG, results in the formation of the first porphyrin of the pathway, namely uroporphyrinogen (UPG). Condensation occurs in a head- to-tail manner, so that a linear tetrapyrrole is produced; this is named as hydroxy methyl bilane (HMB). The enzyme for this reaction is PBG-deaminase (otherwise called Uroporphyrin I synthase or HMB synthase). HMB molecule will cyclise spontaneously to form uroporphyrinogen I. It is converted to uroporphyrinogen

III by the fusion occurs, the III series of isomers are predominantly formed; and only the III series are further utilized. The pyrrole rings are joined together by methylene bridges (-CH2-), which are derived from the alpha carbon of glycine. During this deamination reaction 4 molecules of ammonia are removed Porphyrinogens are colorless, but are readily oxidized to porphyrins, which are colored compounds.

Step 4: Synthesis of CPG

The UPG-III is next converted to coproporphyrinogen (CPG-III) by decarboxylation. Four molecules of CO2 are eliminated by uroporphyrinogen decarboxylase. The acetate groups (CH2–COOH) are decarboxylated to methyl (CH3) groups

Step 5: Synthesis of PPG

Further metabolism takes place in the mitochondria. CPG is oxidized to protoporphyrinogen (PPG-III) by coproporphyrinogen oxidase. This enzyme specifically acts only on type III series, and not on type I series. Two propionic acid side chains are oxidatively decarboxylated to vinyl groups. This reaction requires molecular oxygen.

Step 6: Generation of PP

The Protoporphyrinogen-III is oxidized by the enzyme protoporphyrinogen oxidase to protoporphyrin- III (PP-III) in the mitochondria. The oxidation requires molecular oxygen. The methylene bridges (–CH2) are oxidised to methenyl bridges (–CH=) and colored porphyrins are formed. Protoporphyrin-9 is thus formed.

Step 7: Generation of Heme

The last step in the formation of heme is the attachment of ferrous iron to the protoporphyrin. The enzyme is heme synthase or ferrochelatase which is also located in mitochondria. Iron atom is coordinately linked with 5 nitrogen atoms (4 nitrogen of pyrrole rings of protoporphyrin and 1st nitrogen atom of a histidine residue of globin). The remaining valency of iron atom is satisfied with water or oxygen atom.

When the ferrous iron (Fe++) in heme gets oxidized to ferric (Fe+++) form, hematin is formed, which loses the property of carrying the oxygen. Heme is red in color, but hematin is dark brown.

Disorders of Heme Synthesis

Porphyrias are a group of inborn errors of metabolism associated with the biosynthesis of heme. These are characterized by increased production and excretion of porphyrins and/or their precursors (ALA + PBG). Most of the porphyrias are inherited as autosomal dominant traits.

Porphyrias may be broadly grouped into 3 types:

a. Hepatic porphyrias

b. Erythropoietic porphyrias

c. Porphyrias with both erythropoietic and hepatic abnormalities.

This classification is based on the major site, where the enzyme deficiency is manifested. The clinical manifestations vary. Porphyrias in general, are not associated with anemia.

PBG = Porphobilinogen; CP = Coproporphyrin; ALA = delta amino levulinic acid; UP = uroporphyrins.

Type	Enzyme defect	Inheritance	Excretion in urine	Other salient features
Acute intermittent porphyria (AIP)	**PBG-deaminase (UPG-1 synthase) (enzyme 3)**	**Autosomal dominant**	**Precursors, ALA and PBG. No color on voiding**	**Most common porphyria (1 in 10,000). Hepatic porphyria. Abdominal and neurological manifestations. No photosensitivity.**
Congenital erythro-poietic porphyria	UPG-cosynthase (enzyme 3b)	Autosomal recessive	UP and CP; Port-wine appearance	Marked photosensitivity. Erythrodontia Incidence, rare.
Porphyria cutanea tarda	UPG-decarboxy-lase (enz 4)	Autosomal dominant	Uroporphyrins Urine colored.	Second most common; incidence 1 in 25,000. Photosensitivity.
Hereditary copro-porphyria	CPG-III-oxidase (enzyme 5)	Autosomal dominant	UP and CP excreted in urine and feces. Colored urine.	Symptoms similar to AIP; but milder. Photosensitivity is also seen.
Hereditary proto-porphyria	Heme synthase or Ferrochelatase (enzyme 7)	Autosomal dominant	Neither porphyrins nor precursors are excreted in urine.	Protoporphyrin increased in plasma, RBCs and feces. RBCs show fluorescence.

Enzyme deficiencies in porphyrias

Disorders of Haem Metabolism: Iron and The Porphyrias

Iron is an essential element present mainly in the porphyrin complex, haem, and in iron storage proteins, ferritin and haemosiderin. Haem, which is present in haemoglobin (Hb), myoglobin and cytochromes, is formed by the insertion of ferrous iron, Fe^{2+}, into protoporphyrin, which itself is synthesised by a complex chain of reactions.

Iron Metabolism

The adult human possesses about 70 mmol (4 g) of iron. Iron balance is regulated by alterations in the intestinal absorption of iron. There is only a limited capacity to increase or decrease the rate of loss of iron.

Dietary Iron and Iron Absorption

The normal intake of iron is about 0.2–0.4 mmol/day (10–20 mg/day). Good sources are liver, fish and meat. Normally, about 5–10% of dietary iron is absorbed by an active transport process. Most absorption occurs in the duodenum. The rate of absorption is controlled by physiological and dietary factors:

• State of iron stores in the body: Absorption is increased in iron deficiency and decreased when there is iron overload. The mechanism is unclear.

• Rate of erythropoiesis: When this rate is increased, absorption may be increased even though the iron stores are adequate or overloaded.

• Contents of diet: Substances that form soluble complexes with iron (e.g. ascorbic acid) facilitate absorption. Substances that form insoluble complexes (e.g. phytate) inhibit absorption.

• The chemical state of the iron: Iron in the diet does not usually become available for absorption unless released during digestion. This depends, at least partly, on gastric acid production; Fe^{2+} is more readily absorbed than Fe^{3+}, and the presence of H^+ helps to keep iron in the Fe^{2+} form. Iron in haem (in meat products) can be absorbed while still contained in the haem molecule.

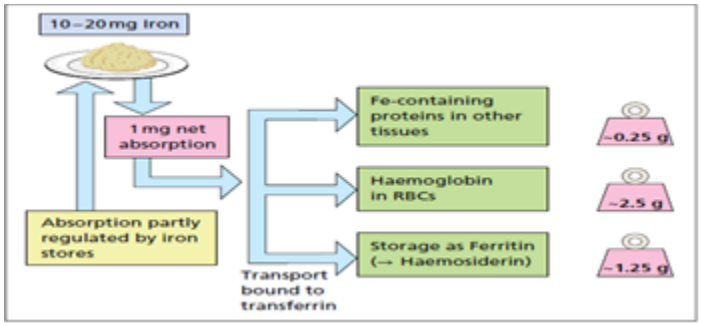
Iron Transport, Storage and Utilization

After being taken up by the intestinal mucosa, iron is either (1) incorporated into ferritin and retained by the mucosal cells, or (2) transported across the mucosal cells directly to the plasma, where it is carried mainly combined with transferrin.

Iron retained by mucosal cells is lost from the body when the cells are sloughed. Mucosal cell retention is influenced by the body's iron status, being reduced in iron depletion and increased in states of iron overload. The total iron circulating bound to transferrin is normally about 50–70 μmol (3–4 mg). Iron in plasma is taken up by cells and either incorporated into haem or stored as ferritin (or haemosiderin, probably formed by the condensation of several molecules of ferritin). Iron released by the breakdown of Hb, at the end of the erythrocyte's life, is normally efficiently conserved and later reused.

Iron excreted in the faeces is principally exogenous, that is, dietary iron that has not been absorbed by the mucosal cells and transported into the circulation. In males, there is an average loss of endogenous iron of about 20 μmol/day (1 mg/day) in cells desquamated from the skin and

the intestinal mucosa. Females may have additional losses due to menstruation or pregnancy. Urine contains negligible amounts of iron.



Serum Iron

Serum iron determination is only required for diagnostic purposes for a few conditions, for example in suspected cases of acute iron poisoning and in the assessment of individuals with an increased risk of haemochromatosis.

Serum Ferritin

Serum ferritin closely reflects body iron stores, unlike serum iron which changes only in severe abnormalities. Low or low-normal ferritin indicates depleted iron stores. Ferritin may be falsely elevated in inflammation, cancer, or liver disease because it is an acute-phase reactant. High ferritin suggests iron overload, though it can also occur in liver disease or malignancy. Overall, serum ferritin is the most useful routine test for assessing iron status.

Serum Transferrin, Total Iron-Binding Capacity and Iron Saturation

Normally, transferrin accounts for almost all serum iron-binding capacity, with about 40% of its sites occupied by iron, and it shows minimal short-term variation.

Transferrin levels decrease in PEM, acute inflammation, infection, cancer, and chronic liver disease, but increase in iron deficiency.

Transferrin can be measured directly or indirectly as total iron-binding capacity (TIBC), and saturation depends on the ratio of serum iron to transferrin.

In iron-deficiency anaemia, low serum iron with high transferrin causes low TIBC saturation, while iron overload shows high saturation, especially in haemochromatosis (>60%).

TIBC saturation is useful for detecting early haemochromatosis, guiding iron therapy in chronic renal failure, and differentiating haemochromatosis from malignancy in patients with high ferritin.

Iron Deficiency

Worldwide, this is the most common single nutrient deficiency. The main causes are deficient intake (including reduced bioavailability due to dietary fibres, phytates, etc.), impaired absorption (e.g. intestinal malabsorptive disease, abdominal surgery) and excessive loss (e.g. menstrual, GI bleeding). In patients who develop iron deficiency,

• serum ferritin falls, then

• serum transferrin and TIBC increase, after which

• serum iron falls, and finally

• anaemia becomes evident.

A microcytic, hypochromic anaemia is characteristic, and storage iron is absent from macrophages in the bone marrow aspirate. In general, serum ferritin is the best diagnostic test for iron deficiency (renal failure is one of the few exceptions.

Biochemical tests may help to identify the underlying cause of iron deficiency anaemia. For example, practice guidelines recommend that where GI investigations are indicated, patients should be screened for coeliac disease (Chapter 14: Small intestine and colon/Serological tests for coeliac disease) as a possible cause of malabsorption. It should be noted that the traditionally widely used guaiac-based FOB tests are not sufficiently sensitive for excluding the possibility of GI blood loss in this setting and a negative result can give false reassurance and may delay diagnosis. However, there is potential for the use of quantitative faecal immunochemical tests (FITs) for haemoglobin to guide referral and further investigations in symptomatic patients presenting to primary care (Chapter 14: Small intestine and colon/Gastrointestinal inflammation).

Iron Poisoning

This is potentially life threatening, particularly in children. Early clinical symptoms, which include epigastric pain, nausea and vomiting, often with hematemesis, may settle but be followed later by acute encephalopathy and circulatory failure. Acute liver and renal failure may also develop. Treatment involves giving desferrioxamine, an iron-chelating agent, which binds the iron in plasma, and the resulting complex is excreted in urine. Serum iron values greater than 90 μmol/L require treatment. An immediate IM injection of desferrioxamine is followed by gastric lavage, leaving desferrioxamine in the stomach.

Porphyrin Metabolism

Porphyrins are tetrapyrrole compounds involved in haem synthesis, with haem formed by the combination of Fe^{2+} and protoporphyrin IX, mainly in the liver and bone marrow.

Defects in enzymes of the haem biosynthetic pathway cause accumulation of intermediates, leading to a group of rare disorders called porphyrias.

Porphyrias are classified into acute, cutaneous, or mixed types, and only a minority of affected individuals develop symptoms.

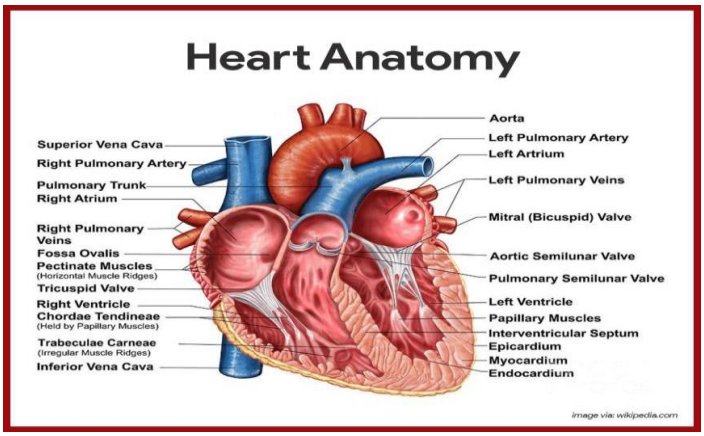
Abnormal Derivatives of Haemoglobin

These all reduce the oxygen-carrying capacity of the blood. The abnormal derivatives of Hb can all be identified by means of their characteristic absorption spectra, and it is possible to measure the various derivatives quantitatively if they are present in sufficient amounts.

Cardiovascular Disorders

The heart is a muscular organ found in humans and other animals. This organ pumps blood through the blood vessels. The heart and blood vessels together make the circulatory system. The pumped blood carries oxygen and nutrients to the tissue, while carrying metabolic waste such as carbon dioxide to the lungs. In humans, the heart is approximately the size of a closed fist and is located between the lungs, in the middle compartment of the chest, called the mediastinum.

In humans, the heart is divided into four chambers: upper left and right atria and lower left and right ventricles. Commonly, the right atrium and ventricle are referred together as the right heart and their left counterparts as the left heart. In a healthy heart, blood flows one way through the heart due to heart valves, which prevent backflow. The heart is enclosed in a protective sac, the pericardium, which also contains a small amount of fluid. The wall of the heart is made up of three layers: epicardium, myocardium, and endocardium.



Cardiovascular Disease (CVD)

 Global Impact:
- CVD is the leading cause of death worldwide.
- Since 1990, it has caused more deaths than any other illness, including infectious diseases.
- Over 75% of CVD deaths are due to coronary artery disease (CAD) and stroke.

 Major Risk Factors:
- Lifestyle: smoking, obesity, physical inactivity.
- Medical: high cholesterol, high blood pressure, poorly controlled diabetes.
- Other contributing factors: age, family history, and stress.

 Symptoms:
- Often silent for long periods.
- Can eventually present as chest pain (angina) or shortness of breath.
- Symptom overlap makes early recognition difficult.

 Coronary Heart Disease (CHD):
- Leading cause of CVD deaths: ~3.8 million men and 3.4 million women die annually.
- Incidence is falling in some high-income countries but rising in low- and middle-income countries, accounting for >60% of global CHD burden.

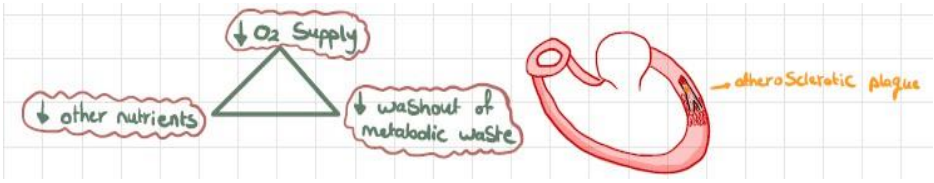
 Valvular Heart Disease:
- Common worldwide, but causes vary by region.
- South Asia & Africa: mostly due to rheumatic fever.
- High-income countries: mostly calcific aortic valve disease.

 Challenges in Detection:
- CVD is often clinically silent, so advanced disease may develop before symptoms appear.
- Limited diversity of symptoms means different heart problems can look similar, delaying diagnosis.

Ischaemic Heart Disease

Ischaemic heart disease (IHD) is an acute or chronic disease of the heart muscle caused by insufficient blood supply in coronary artery disease. The involvement of coronary arteries can be organic (narrowing), functional (spasm) or thrombotic (mural or obturating thrombus).

Ischemia is reduced blood flow



Isolated hypoxemia is only oxygen supply is reduced and blood flow is normal → nutrient supply & washout of metabolic waste is normal, e.g -severe anemia, severe pulmonary disease, cyanotic heart disease (shunting in the heart), 1schemic heart disease mainly occur in left ventricle or right ventricle (IHD. 99% mainly occur in left ventricle) only 1- 2 % of cases right ventricular ischemia may occur especially when there is right ventricular hypertrophy, for example in cor pulmonale and when blood flow to the right coronary artery is reduced.

right Ventricle	Left ventricle
① has thickness about 0.3 - 0 .5 Cm (↓O_2 needs) ②When contract, has to generate lower pressure in the wall (0- 25Hg) □ ↓ work → ↓O_2 needs □ Squeezes its own microcirculation with so more tension so of supply O_2 supply in systole in systole become less for itself ③ receives blood supply during diastole and systole	① has thickness about 1 .5 cm (↑ O_2 needs) ②When contract, has to generate higher pressure so there is higher tension in the wall (0-125 Hg) □ ↑ work→O_2 needs □ it impedes its own microcirculation with more tension so of supply in systole become less for itself ③ blood flow to left ventricle is only during diastole

Causes of IHD

- **Atherosclerosis**

Atherosclerosis is a degenerative involvement of arterial walls characterized by the accumulation of lipids, inflammatory infiltration of the vessel wall and fibrous tissue proliferation. After birth, human arteries are smooth, elastic and not very resistant to the blood flow.

The most common cause of IHD is atherosclerosis of the coronary arteries. At the beginning, atherosclerotic plaque build-up is usually associated with an enlarged arterial diameter (arterial remodeling), and the disease may be present without clinical symptoms for decades.

Only when the plaque narrows the arterial lumen to more than 70 %, does stenosis start to obstruct increased coronary flow under physical strain. This is how ischaemia is formed downstream the obstruction with its clinical symptoms in the form of exertional angina pectoris (chest pain on physical exertion).

Arterial Lumen Narrowing	Grade of Coronary Atherosclerosis
25 %	Grade I
50 %	Grade II
75 %	Grade III
over 75 %	Grade IV

Another mechanism for initiating ischaemia is a spasm of the smooth muscle of the arterial wall. It is based on endothelial dysfunction induced by stimuli such as cold, tobacco smoke, physical and mental strain.

Should the plaque rupture, the thrombogenic (subendothelial) structures of the vessel wall become exposed, which leads to platelet activation and blood clotting which may even cause a sudden closure of the coronary artery. Bleeding in the plaque may also lead to a sudden arterial narrowing and a dramatic decrease in the blood flow. These conditions cause acute coronary syndromes. Atherosclerosis may affect all of the three major arteries evenly, however prevailing involvement of one of them is more common.

Heart arteries most commonly affected by atherosclerosis:

• RIA, ramus interventricular is anterior (ventralis) arteriae coronariae cordis sinistrae (ACS);

• RCx, ramus circumflexus arteriae coronariae cordis sinistrae;

• ACD, arteria coronaria cordis dextra.

Coronary atherosclerosis may build up evenly (concentrically) around the arterial perimeter, followed by the residual lumen is in the middle of the artery. However, the plaque may also be asymmetric (eccentric), outside the centre. The grade of atherosclerosis is assessed depending on the percentage of arterial lumen narrowing by sclerotic plaques. Coronary artery diseases other than atherosclerosis are rare (e.g. Wegener's granulomatosis, syphilis). The risk factors for coronary atherosclerosis are the same as the risks for atherosclerosis in general. They do not exactly explain the cause of atherosclerosis however do help estimate the risk of complications associated with atherosclerosis (cardiovascular risk). Therapy is used for prevention. For many years, atherosclerosis was regarded as a mechanical process typical of lipid accumulation in the vessel wall, and calcium incrustation at a later phase. Multifactorial aetiology of atherosclerosis is accepted at present. Risk

factors have been shown to contribute to atherosclerosis. The first stages of atherosclerosis are known to be caused by increased penetration and infiltration of atherogenic lipoproteins and inflammatory cells from the blood through the endothelium, followed by their accumulation in the subendothelial space. At later stages, fibro productive processes join the process of atherogenesis in reaction to depositing lipids and the inflammatory infiltration of the vessel wall. Endothelial damage, inflammatory mechanisms and atherogenic lipoproteins are involved to varying degrees in the development of these lesions. All of these factors are in complicated interactions and potentiate each other.

Uncontrollable Risk Factors	Controllable Risk Factors
Age (men over 45, postmenopausal women or over 55)	Smoking
Male gender	Dyslipidaemia, increased total plasma cholesterol (LDL--cholesterol in particular), increased triacylglycerols, decreased HDL-cholesterol)
Family history of premature IHD (manifested in men under 55 and women under 65), or other clinical manifestations in first-degree relatives (parents, siblings and children)	Hypertension
	Glucose metabolism disorders (diabetes mellitus, boundary fasting blood glucose, impaired glucose tolerance)
	Obesity (android type)

- **Acute Forms of Ischaemic Heart Disease**

Acute coronary syndrome is the clinical manifestation of a critical phase in IHD development, when the imbalance between the oxygen supply and requirements of the myocardium for the supply and removal of metabolic waste products becomes manifested.

The most common pathophysiological background for these conditions is an atherosclerotic plaque rupture and a blood clot formation in the coronary artery with potential presence of coronary spasm. The blood clot leads to a narrowing or closure of the coronary artery with varying degrees of seriousness, and embolism in its peripheral branches.

• ST-segment elevation myocardial infarction (STEMI);

• Non-ST-segment elevation myocardial infarction (NSTEMI);

• Unstable angina pectoris.

1- Unstable Angina Pectoris

Unstable angina pectoris is not a homogeneous nosological entity, but rather a syndrome with a name describing the acute condition. Clinical definition of unstable angina pectoris – criteria:

• Newly developed angina pectoris; or

• Sudden worsening of existing angina pectoris; or

2- Myocardial Infarction

Myocardial infarction is reserved for conditions with evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Necrosis assumes a coagulative character, caused by high protein content. Around 20 hours from the start of ischaemia, the colour of the tissue turns to yellowish, and water loss shrinks the necrotic tissue volume. Fully developed necrosis is evident after 3 days.

• Development of stenocardia in the subacute MI phase.

Worsening means more frequent anginous attacks (frequent stenocardia), more intense pain or change in the nature of attacks, stenocardia while at rest or protracted stenocardia. The difference from non-ST elevation MI consists in the absence of laboratory markers of myocardial necrosis. The ECG only shows signs indicative of subendocardial ischaemia.

- **Chronic Forms of Ischaemic Heart Disease**

1- Exertional (Stable) Angina Pectoris

The typical clinical symptom is pain behind the breastbone in situations connected to increased oxygen consumption in the myocardium. Stenocardia usually lasts less than 20 minutes, radiates to the left arm, neck and back, and is usually not accompanied by vegetative symptoms. There is also a painless form of stable angina pectoris, most often manifested by dyspnoea.

Precipitating moments include physical exertion, heavy food or emotions. Discomfort is more pronounced in cold weather, or in the morning in some patients (quite typically when coming out from a warm environment to the freezing air). Discontinued exertion or nitrate administration led to relief within minutes.

2- Variant Angina Pectoris (Prinzmetal's Vasospastic Angina)

Variant angina pectoris is a nosological entity, the pathophysiological background of which is spasms of epicardial coronary arteries caused by endothelial dysfunction.

The typical clinical symptom is stenocardia while at rest accompanied by transient ST-segment elevations and heart rhythm disorders. The spasms can be induced during coronarography examination by provocation tests. If no spasm is present on physical exertion, the patient is usually asymptomatic. Variant angina typically affects women at an age between 40–50 years with some risk factors of ischaemic heart disease.

3- Cardiac Syndrome X

This name includes a heterogeneous group of patients with typical exertional stenocardia and evidence of ischaemia on a stress ECG or thallium myocardial scintigraphy, but without the presence of stenotic alterations or spasm on coronary arteries. Microvascular dysfunction at the level of prearterioles with the impossibility to increase coronary perfusion on exertion is being considered as one of causes.

Heart Failure

1- Acute Heart Failure

Acute heart failure is a sudden severe heart disorder or a sudden worsening of the heart's function where the heart is unable to pump blood from the venous circulation to the lungs, or from the lungs to the arterial circulation. This results in congestion of the blood in some organs and insufficient tissue oxygenation. Many cardiovascular diseases present themselves as acute heart failure. Depending on the dominant clinical symptoms, heart failure may be right-sided or left-sided

Acute left-sided heart failure

Acute left-sided heart failure occurs as a result of sudden injury to the left ventricle by mechanical influences, direct injury or impaired diastolic filling.

This failure leads to sudden left ventricular pulmonary hypertension, which transmits back to the left atrium and pulmonary circulation. This leads to acute pulmonary hypertension and the amount of blood in the lungs rises. If pulmonary capillary pressure exceeds colloid osmotic pressure in the plasma, liquid penetrates into the interstitium followed by to the alveoli. This is why interstitial and intra-alveolar pulmonary oedemas are recognized.

Typical symptoms of acute left ventricular failure include dyspnoea and pulmonary oedema. Pulmonary oedema is a symptom of acute left-sided heart failure. The patient is extremely dyspnoeic even at rest, tachypnoic, anxious, restless, pale, perspiring and coughs up frothy sputum.

Cardiac asthma (asthma cardiale) is a condition of severe dyspnoea usually occurring at night when it wakes up the patient, who is first urged to sit up, then stand up and breathe while employing accessory muscles.

2-Chronic Heart Failure

Chronic heart failure is a disorder of the heart's performance, whereby the minute cardiac output decreases despite sufficient filling of the ventricles, and the heart is unable to cover the metabolic requirements of peripheral tissues.

Depending on whether congestion prevails in the pulmonary or systemic bloodstream, heart failure is sometimes classified as right-sided and left-sided. This does not indicate, however, which of the ventricles is affected more. Chronic heart failure develops as a result of systolic and/or diastolic myocardial dysfunction. The most common cause is IHD, less frequently cardiomyopathies, myocarditis and toxic myocardial injuries. Worsening factors include hypertension, some arrhythmias, anaemia, hyperthyroidism or the iatrogenic effects of some drugs (antidepressants).

The basic pathophysiological cause of chronic heart failure development is a disorder of systolic or diastolic function of the ventricles with a subsequent drop in tissue perfusion, which induces the activation of sympathetic nerves, the renin-angiotensin-aldosterone system and the secretion of endothelin and vasopressin. The myocardium undergoes remodeling (presented as dilation at the ventricular level) which worsens contractility and relaxation of cardiomyocytes, and ligament restructuring and collagen proliferation in the interstitium. Disorders of endothelial functions and microvascular fibrosis occur in the vascular blood stream. The heart is no longer able to increase its performance on exertion despite the fact that the ventricular dilation allows the stroke volume to be kept with an even lower ejection fraction (EF is less than 45 %).

Left-sided heart failure

Most signs and symptoms occur as a result of blood congesting in the lungs, namely exertional dyspnoea, paroxysmal nocturnal dyspnoea (cardiac asthma), and pulmonary oedema. Objective signs include wet inspiratory crackles not changing their character after coughing, and also a one-sided or two-sided effusion.

Right-sided heart failure

Most symptoms occur as a result of blood congesting before the right ventricle, increased filling of the jugular veins, positive hepatojugular reflux, hepatomegaly and peripheral oedemas. Oedemas first develop around the ankles, form during the day and release at night (nocturia). They signal a 3–5-litre increase in the volume of extracellular fluid. Extreme retention of fluids manifests itself as hydrothorax, ascites, anasarca, and hydropericardium.