Title:

L1&2: Water Homeostasis

Name of the instructor:

Assist.prof.Dr. Huda farhan ahmed

Target population:

Students of the third stage of medical laboratories

Introduction:

Water is an essential body constituent, and homeostatic processes are important to ensure that the total water balance is maintained within narrow limits, and the distribution of water among the vascular, interstitial and intracellular compartments is maintained.
The body maintains a balance of water intake and output by a series of negative feedback loops involving the endocrine system and autonomic nervous system.

Pretest:

What is the cell membrane or plasma membrane made of?

Scientific Content: Water Homeostasis

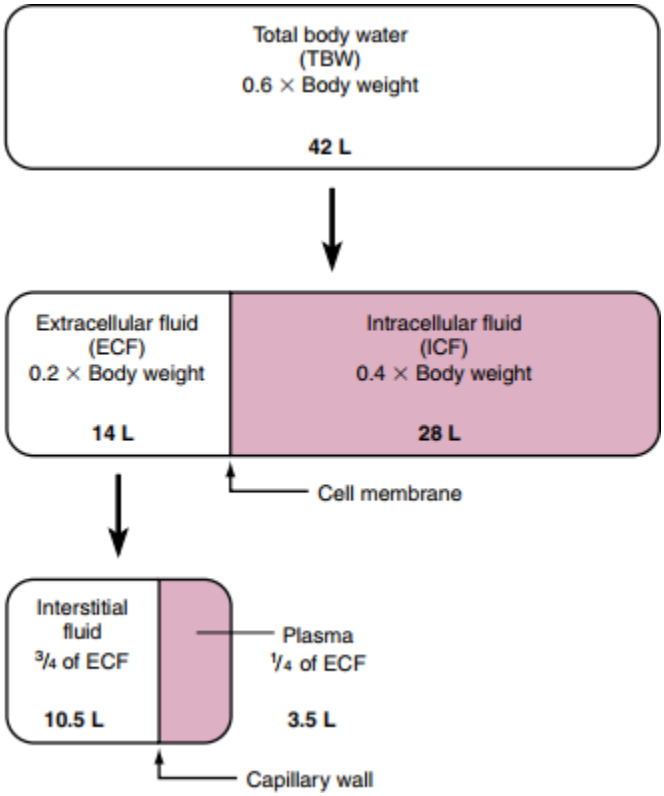
Water is an essential body constituent, and homeostatic processes are important to ensure that the total water balance is maintained within narrow limits, and the distribution of water among the vascular, interstitial and intracellular compartments is maintained.
The body maintains a balance of water intake and output by a series of negative feedback loops involving the endocrine system and autonomic nervous system.

Distribution of Water:

In a 70-kg man, the Total Body Water (TBW) is about 42 L and contributes about 60 per cent of the total body weight.
Two thirds of the water are in the Intra Cellular Fluid (ICF), and one third is in the Extra Cellular Fluid (ECF). Because the plasma membrane of most cells is highly permeable to water, ICF and ECF are in osmotic equilibrium. The ECF is divided into a vascular compartment (plasma) and an interstitial fluid compartment.

Expressed as percentages of body weight, the volumes of total body water, ICF, and ECF are:

Total body water = 0.6 × (body weight)
ICF = 0.4 × (body weight)
ECF = 0.2 × (body weight)



Water Intake—Water is supplied to the body by the following processes:

a. Dietary liquids

b. Solid foods

c. Oxidation of foodstuffs: It is obtained from the combustion of fats, proteins and carbohydrates. The oxidation of fats yields 107 ml/100 gm, proteins 41 ml/100 gm and carbohydrates 56 ml/100 gm.

Water output: Water is lost from the body by the following routs:

a. Urine

b. Respiration

c. Lactation

d. Faeces

e. Evaporation from skin and lungs

f. Eyes (tears)

FUNCTIONS OF WATER

1. *Solvent:* One of the most important properties of water is its capacity to dissolve different kinds of substances. It is therefore the most suitable solvent for cellular components. Water brings together various substances in contact when chemical reactions take place.

2. *Catalytic action:* Water accelerates a large number of chemical reactions in the body due to its ionizing power.

3. *Lubricating actions:* Water acts as a lubricant in the body and prevents friction in joints, pleura, conjunctiva, and peritoneum.

4. *Heat regulation:* By virtue of its high specific heat, water prevents any significant rise in the body temperature due to heat liberated from body reactions. The loss of heat from the body is also regulated by the evaporation of water from skin and lungs and its removal in urine.

The balance sheet of water intake and loss is given as:

Water intake			*Water loss*		
Drinks	48 %	1350 ml	Lungs	12%	500 ml
Solid	40 %	900 ml	Skin	24%	700 ml
Oxidation of food	12%	450 ml	Urine	56%	1400 ml
			Faeces	08%	100 ml
	100%	2700 ml		100%	2700 ml

Disturbances of Water Homeostasis

- Gain or loss of extracellular fluid volume.
- Gain or loss of solute.

In many instances disturbances of water homeostasis involve imbalances of both volume and solutes.

Four specific examples of water homeostasis:
- Hypervolemia
- Overhydration
- Hypovolemia
- Dehydration

Hypervolemia: • occurs when too much water and solute at the same time. Although extracellular fluid volume increases, plasma osmolarity may remain normal.

Overhydration: • occurs when too much water is taken by drinking without solute, volume increases, but because solute is not present, plasma osmolarity decreases.

Hypovolemia: • occurs when water and solutes are lost at the same time. This condition primarily involves a loss of plasma volume. Plasma osmolarity usually remains normal even though volume is low. Too much IV fluids can increase plasma volume dramatically, but with an isotonic solution the plasma osmolarity would remain normal and result in hypervolemia.

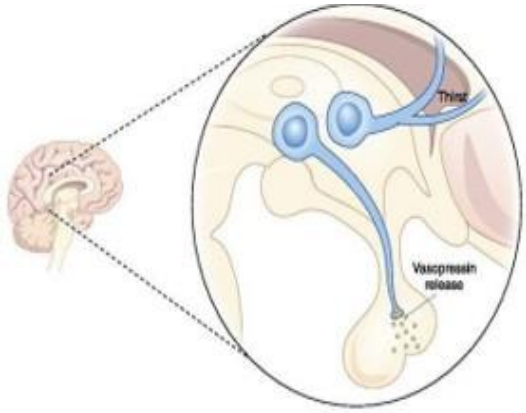
Dehydration: • When water, but not solute, is lost, dehydration occurs. Dehydration involves a loss of volume but, because solutes are not lost in the same proportion, plasma osmolarity increases. Although sweating causes the loss of some solute through the skin, much more water is lost, and the person becomes dehydrated.

Mechanisms of Fluid Balance

• The body have mechanisms that regulate fluid levels within a narrow range, the body fluids remain within certain physiological limits, an important aspect of homeostasis, four primary mechanisms regulate fluid homeostasis:
-Antidiuretic hormone or ADH
-Thirst mechanism
-Aldosterone
-Sympathetic nervous system
• Three of these mechanisms involve the kidneys.

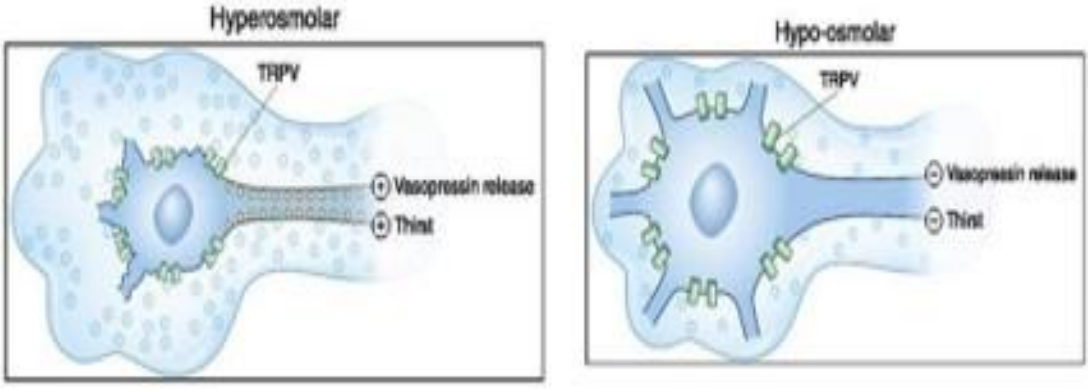
Effect of ADH

• When loses water by sweating, his plasma becomes more concentrated in solutes.
• Osmoreceptors in the hypothalamus detect the increased osmolarity or concentration of solutes in the plasma.
• In response to this increased concentration, the antidiuretic hormone is released into the blood at posterior pituitary.
• The target tissue for ADH is the late distal convoluted tubule and collecting duct cells in the kidney.



Thirst Mechanism

• The thirst mechanism is the primary regulator of water intake and involves hormonal and neural input as well as voluntary behaviors.
• There are three major reasons why dehydration leads to thirst:
1. When saliva production decreases, the mouth and throat become dry. Impulses go from the dry mouth and throat to the thirst center in the hypothalamus, stimulating that area.
2. When you are dehydrated, blood osmotic pressure increases, stimulating osmoreceptors in the hypothalamus and the thirst center in the hypothalamus is now further activated.
3. Decreased blood volume causes a decrease in blood pressure that stimulates the release of renin from the kidney. This causes the production of angiotensin II which stimulates the thirst center in the hypothalamus.
• Stimulation of the thirst center in the hypothalamus gives you the desire to drink.



Results of Fluid Ingestion
• This fluid ingestion:
1. Relieves the dryness in the mouth and throat.
2. Fluid ingestion also stimulates stretch receptors in the stomach and intestine to send inhibitory signals to the thirst center.
3. When normal fluid volume is restored, dehydration is relieved. Renin secretion from the kidney and angiotensin II now decreases to baseline levels.

Posttest

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What are the mechanisms of fluid balance?

References:

Clinical Biochemistry (Nanda Maheshwari, MSc (DMLT). Institute of Paramedical Sciences Nanded, Maharashtra, India

Title: =

L 3&4 (Minerals and trace elements metabolism)

Name of the instructor

Assist.prof.Dr. Huda farhan ahmed

Target population:

Students of the third stage of medical laboratories

Introduction:

Minerals are inorganic substances mined from the earth. They are not of plant or animal origin. They exist naturally on and in the earth and many are critical parts of human tissue and are termed “essential” nutrients.
Of the 92 naturally occurring elements, the 14 minerals that have been shown by research to be essential to human health are:
calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, sodium and zinc.

Pretest:

What are the most important minerals and trace elements that the body needs?

Scientific Content: المحتوى العلمي:

Electrolytes and Minerals (Trace Elements) Metabolism

Minerals are inorganic substances mined from the earth. They are not of plant or animal origin. They exist naturally on and in the earth and many are critical parts of human tissue and are termed “essential” nutrients.
Of the 92 naturally occurring elements, the 14 minerals that have been shown by research to be essential to human health are:
calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, sodium and zinc.
Essential macro minerals are those needed in significant quantities (such as calcium) – usually measured in milligrams, and essential trace minerals are those needed in minute quantities (such as selenium) – usually measured in micrograms (one microgram [µcg] equals 1/1,000th of a milligram [mg]).
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**. However, this tiny fraction exerts a tremendous influence on all body functions.
Minerals are required for a variety of physiological functions, their functions are:

1. Maintenance of osmotic pressure of cell
2. Transport of oxygen
3. Growth and maintenance of tissues and bones
4. Working of nervous system
5. Muscle contraction
6. Maintenance of electrolytic balance
7. Acid-base balance

The major elements that compose the human body and their relative amounts are as follows:

Mineral content of human Percent Approximate amount Element body (in gm) in 70 Kg adult. usually measured in micrograms (one microgram [µcg] equals 1/1,000th of a milligram [mg]).

Ca^{++} 1.50 1050

P 1.00 700

K^{+} 0.35 245

Na^{++} 0.15 105

Cl^{-} 0.15 105

Mg^{++} 0.05 035

Fe^{++} 0.004 003

Zn^{++} 0.0033 02

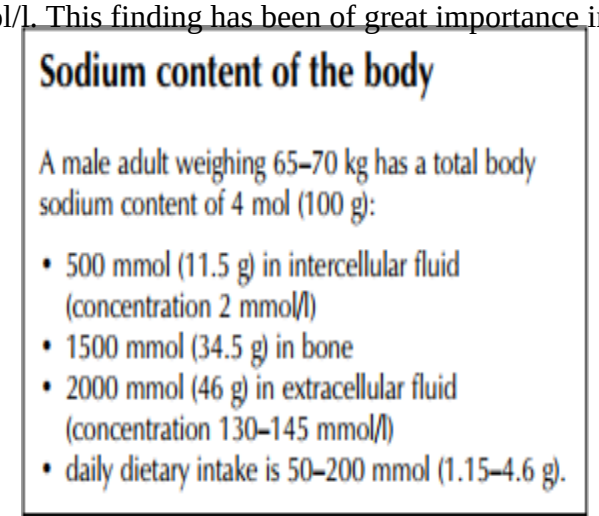
• Quantity elements (electrolytes) — Na (Sodium), Mg (Magnesium), K (Potassium), Ca (Calcium), P (Phosphorus), S (Sulfur), Cl (Chlorine).
• Essential trace elements — Mn (Manganese), Fe (Iron), Co (Cobalt), Ni (Nickel), Cu (Copper), Zn (Zinc), Mo (Molybdenum), Se (Selenium), I (Iodine).
• Function suggested from active handling humans, but no specific identified biochemical functions — Li (Lithium), V (Vanadium), Cr (Chromium), B (Boron), F (Fluorine), Si (Silicon), As (Arsenic).

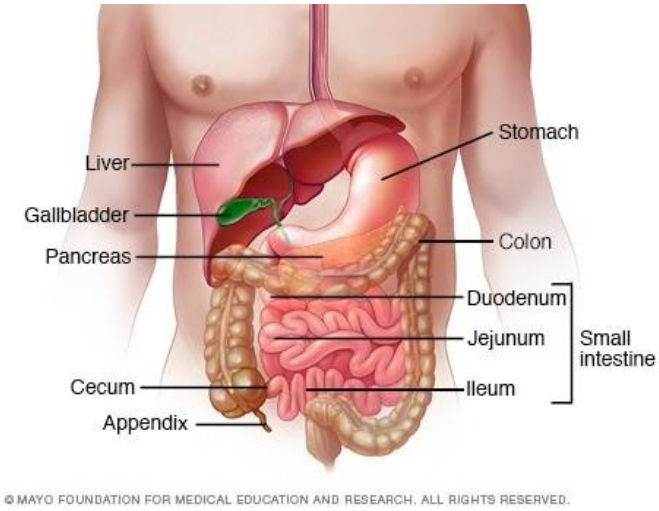
Electrolytes (Na, K, Mg, Ca, Cl)

Sodium (Na^{++}): Sodium is a major cation and contributor to the osmolality of the extracellular fluid of the body, which is one-third of the body water in adults. The sodium content of natural food varies between 0.1 and 3.3 mmol/100 g. In contrast, processed foods have a sodium content of 11–48 mmol/100 g, partly sodium nitrate is used as a preservative.
Sodium is concentrated in the extracellular fluid, giving osmolarity and charge moves from the extracellular fluid into cells there is a change in charge and concentration.

Absorption and availability of sodium

Intestinal sodium absorption is very efficient in both the small intestine and colon. Sodium is absorbed by a variety of processes. In the proximal intestine sodium is absorbed, in part by a solute dependent cotransport system, and is involved in nutrient absorption. In the more distal intestine and colon, sodium absorption is by a sodium/hydrogen interchange; in the colon this process is coupled to chloride/bicarbonate exchange. In the distal intestine and colon, the process is electroneutral and involves protein carriers. In the distal colon active sodium transport occurs against an electrochemical gradient. Water absorption is a passive process that requires active transport of sodium and chloride.
The optimum absorption of water occurs when the concentration of glucose in the intestinal lumen is around 110 mmol/l. This finding has been of great importance in the development of oral replacement solutions (ORS).





Sodium regulation Sodium is found in significant amounts in bone, but this pool is not readily available at times of rapid loss of sodium. The extracellular fluid sodium content is regulated in parallel with the extracellular fluid volume control. When the extracellular fluid or blood volume falls, neural sympathetic activity increases, and the response comprises vasoconstriction, a redistribution of renal blood flow, reduced glomerular filtration, and increased sodium and water retention. In addition, there are increases in renin production, circulating angiotensin II, noradrenaline, adrenaline, ACTH and ADH.

Sodium excretion Sodium is filtered from the plasma in the kidneys, the reabsorption of sodium occurring as an osmotic phenomenon in the proximal tubule, loop of Henle and distal tubule. Distal tubular absorption is very important, and is under the control of atrial natriuretic factor. Renal sodium excretion is also controlled by angiotensin II, prostaglandins and the kallikrein–kinin system.

Sodium depletion Sodium is lost largely via the urine, with only minimal loss occurring via the faeces or skin, unless there are abnormal situations such as diarrhea or excessive sweating. A reduced body sodium pool results in reduced extracellular fluid volume. Increased sodium loss in urine can occur in diseases, e.g., **diabetes mellitus** and **Addison's disease** (adrenal cortical insufficiency), following excessive doses of **diuretic drugs**, and in cases of **renal tubular damage**, as in **chronic renal failure**.
Healthy kidneys maintain a consistent level of sodium in the body by adjusting the amount excreted in the urine. When sodium consumption and loss are not in balance, the total amount of sodium in the body is affected. The concentration of sodium in the blood may be
-Too high (hypernatremia)
-Too low (hyponatremia)

Hypernatremia, the body contains too little water for the amount of sodium. The sodium level in the blood becomes abnormally high when water loss exceeds sodium loss. Usually, hypernatremia results from dehydration. For example, people may lose body fluids and become dehydrated due to:
1-Drinking too little.
2-Vomiting.
3-Having diarrhea.
4-Using diuretics.
5-Sweating excessively.
6-Insufficient water intake usually plays an important role.
People with **diabetes mellitus** and **high blood sugar** levels may urinate excessive amounts, causing dehydration. Dehydration can also be caused by **kidney disorders** and by **diabetes insipidus**, which also causes people to urinate excessive amounts although without high blood sugar levels, and is due to inadequate or ineffective vasopressin secretion or action.

Potassium(k^+): in natural and processed foods the potassium content varies from 2.8 to 10 mmol/kg. Dietary potassium tends to be derived from fresh vegetables and meat. An adult male weight approximately 70 kg contains 2800–3500 mmol (110– 137 g), of which 95% is intracellular (150 mmol/l). Cellular potassium concentrations are affected by **pH, aldosterone, insulin and the adrenergic nervous system**. The plasma concentration of 3.5–4.5 mmol/l is dependent on intake, excretion, and the balance between extracellular and intracellular compartments. There is a direct, reciprocal relationship between plasma potassium and aldosterone production. Control is mainly through urinary loss, with some additional colonic loss. Insulin excretion is increased when the plasma potassium increases, possibly provoking cellular uptake of potassium.

Transport and absorption of potassium: The transport of potassium into cells is under the control of the Na/K-ATPase enzyme, and allows transport of potassium against a concentration gradient. The ratio of extracellular to intracellular potassium concentration is important in the membrane potential difference in neuron and muscle cells (Na^+/K^+-ATPase exchange pump system). Over 90% of dietary potassium is absorbed in the proximal small intestine. In the small intestine potassium absorption is passive, but in the colon, it is an active process. In the sigmoid colon absorption is mediated by a K^+/H^+ mechanism. Body stores of potassium most of the potassium is intracellular, i.e., in the cell fluid compartment.

Potassium is necessary for the normal functioning of cells, nerves, and muscles. The body must maintain the potassium level in blood within a narrow range. A blood potassium level that is
-Too high (hyperkalemia)
-Too low (hypokalemia)

Hyperkalemia, the level of potassium in blood is too high. A high potassium level has many causes, including kidney disorders, drugs that affect kidney function, and consumption of too much supplemental potassium.
Usually, hyperkalemia must be severe before it causes symptoms, mainly abnormal heart rhythms. Doctors usually detect hyperkalemia when blood tests or electrocardiography is done for other reasons.

Causes:
Usually, hyperkalemia results from several simultaneous problems, including the following:
1-**Kidney disorders** that prevent the kidneys from excreting enough potassium
2-**Drugs** that prevent the kidneys from excreting normal amounts of potassium (a common cause of mild hyperkalemia)
3-**A diet high in potassium**
4-**Treatments that contain potassium**
5-**Addison disease** can also cause hyperkalemia.

Hypokalemia, the level of potassium in blood is too low. A low potassium level can make muscles feel weak, cramp, twitch, or even become paralyzed, and abnormal heart rhythms may develop.

Causes
Typically, the potassium level becomes low because too much is lost from the **digestive tract** due to **vomiting, diarrhea, or excessive laxative use**. Sometimes too much potassium is **excreted in urine**, usually because of **drugs** that cause the kidneys to **excrete excess sodium, water, and potassium (diuretics).** In many **adrenal disorders**,

such as **Cushing syndrome,** the adrenal glands produce too much aldosterone, a hormone that causes the kidneys to excrete large amounts of potassium.

Calcium (Ca^{++}): is one of the body's electrolytes, which are minerals that carry an electric charge when dissolved in body fluids such as blood (but most of the body's calcium is uncharged). About 99% of the body's calcium is stored in the bones, but cells (particularly muscle cells) and blood also contain calcium. About 40% of the calcium in blood is attached (bound) to proteins in blood, mainly albumin. Protein-bound calcium acts as a reserve source of calcium for the cells but has no active function in the body. Only unbound calcium affects the body's functions. Calcium is essential for the following:

-Formation of bone and teeth
-Muscle contraction
-Normal functioning of many enzymes
-Blood clotting
-Normal heart rhythm

Calcium absorption and balance

Calcium absorption is largely from the jejunum, but may also occur in the ileum and colon. The predominant absorptive process is by active transport and there is also some simple passive diffusion in the ileum.

Phytate (Phytic acid) binds calcium to form insoluble salts within the intestinal lumen, and reduces calcium absorption. Approximately 60% of the total plasma calcium is filtered in the kidney glomeruli, and in health 97% of this calcium is reabsorbed. Several hormones are involved, including PTH, with increased absorption of calcium and decreased tubular absorption of phosphate.

The level of calcium in blood is regulated primarily by two hormones:

-Parathyroid hormone
-Calcitonin

Too much calcium in the blood is called hypercalcemia.

Too little calcium in the blood is called hypocalcemia.

Hypercalcemia: At first, people have digestive problems, feel thirsty, and may urinate a lot, but if severe, hypercalcemia leads to confusion and eventually coma. If not recognized and treated, the disorder can be life threatening.

Causes: Causes of hypercalcemia include the following:

-**Hyperparathyroidism:** One or more of the four parathyroid glands secrete too much parathyroid hormone, which helps control the amount of calcium in blood.

-**Too much calcium intake:** Occasionally, hypercalcemia develops in people with peptic ulcers if they drink a lot of milk and take calcium-containing antacids for relief. The resulting disorder is called the milk-alkali syndrome.

-**Too much vitamin D intake:** If people take very high daily doses of vitamin D over several months, the amount of calcium absorbed from the digestive tract increases substantially.

-**Cancer:** cells in kidney, lung, and ovary cancers may secrete large amounts of a protein that, like parathyroid hormone, increases the calcium level in blood. Calcium released into the blood when cancer spreads (metastasizes) to bone and destroys bone cells. Such bone destruction occurs most commonly with prostate, breast, and lung cancers. Multiple myeloma (a cancer involving bone marrow) can also lead to the destruction of bone and result in hypercalcemia. Other cancers can increase the calcium level in blood by means not yet fully understood.

-**Bone disorders:** If bone is broken down (resorbed) or destroyed, calcium is released into the blood, sometimes causing hypercalcemia. In Paget disease, bone is broken down, but the calcium level in blood is usually normal. Severe hyperthyroidism can also cause hypercalcemia by increasing resorption of bone tissue.

Hypocalcemia, the calcium level in blood is too low.

A low calcium level may result from a problem with the **parathyroid glands**, as well as **from diet**, **kidney disorders**, or **certain drugs**. As hypocalcemia progresses, muscle cramps are common, and people may become confused, depressed, and forgetful and have tingling in their lips, fingers, and feet as well as stiff, achy muscles.

Usually, the disorder is detected by routine blood tests. Calcium and vitamin D supplements may be used to treat hypocalcemia.
Thus, hypocalcemia causes problems only when the level of unbound calcium is low. Unbound calcium has an electrical (ionic) charge, so it is also called ionized calcium.

Magnesium (Mg^{++}): is one of the body's electrolytes, which are minerals that carry an electric charge when dissolved in body fluids such as blood, but the majority of magnesium in the body is uncharged and bound to proteins or stored in bone. Bone contains about half of the body's magnesium. Blood contains very little. Magnesium is necessary for the formation of bone and teeth and for normal nerve and muscle function.

Many enzymes in the body depend on magnesium to function normally. Magnesium is also related to the metabolism of calcium and the metabolism of potassium. The level of magnesium in the blood depends largely on how the body obtains magnesium from foods and excretes it in urine and stool and less so on the total body stores of magnesium. The level of magnesium in the blood can become

-Too high (hypermagnesemia)
-Too low (hypomagnesemia)

Hypermagnesemia, the level of magnesium in blood is too high. Hypermagnesemia is uncommon. It usually develops only when people with kidney failure are given magnesium salts or take drugs that contain magnesium (such as some antiacids or laxatives). Hypermagnesemia may cause

-Muscle weakness
-Low blood pressure
-Impaired breathing

When hypermagnesemia is severe, the heart can stop beating.

Hypomagnesemia, the level of magnesium in blood is too low.

Causes
Usually, the magnesium level becomes low because people consume less (most often, because of starvation) or because the intestine cannot absorb nutrients normally (called malabsorption). But sometimes hypomagnesemia develops because the kidneys or intestine excrete too much magnesium.
Hypomagnesemia may also result from the following:
-**Consuming large amounts of alcohol (common),** which reduces consumption of food (and thus magnesium) and increases excretion of magnesium
-**Protracted diarrhea** (common), which increases magnesium excretion
-**High levels of aldosterone, vasopressin (antidiuretic hormone), or thyroid hormones**, which increase magnesium excretion
-**Drugs** that increase magnesium excretion, including diuretics, the antifungal drug amphotericin B, and the chemotherapy drug cisplatin
-**Breastfeeding**, which increases requirements for magnesium

CHLORIDE (Cl^-)
Chloride concentration in plasma is 96-106 mEq/L and in Cerebrospinal fluid (CSF), it is about 125 mEq/L. Chloride concentration in CSF is higher than any other body fluids. Since CSF protein content is low. Renal threshold for Cl^- is about 110 mEq/L. Daily excretion of Cl^- is about 5-8 gm/day**.**
Intake, output and metabolism of sodium and chloride run in parallel. The homeostasis of Na^+, K+ and Cl^- are inter-related. Chloride is important in the formation of hydrochloric acid in gastric juice.
Hyperchloremia is seen in:
1. Dehydration

2. Cushing's syndrome. Mineralocorticoids cause increased reabsorption from kidney tubules.
3. Severe diarrhea leads to loss of bicarbonate and compensatory retention of chloride.
4. Renal tubular acidosis.

Hypochloremia:

Causes

1. Excessive vomiting. HCl is lost, so plasma Cl^- is lowered. There will be compensatory increase in plasma bicarbonate. This is called hypochloremia alkalosis.
2. Excessive sweating.
3. In Addison's disease, aldosterone is diminished, renal tubular reabsorption of Cl^- is decreased, and more Cl^- is excreted.

Manganese (Mn): Manganese content of foods varies greatly. found the highest concentrations in nuts, grains, and cereals; the lowest in dairy products, meat, poultry, fish, and seafood. Relatively high concentrations of manganese were found in soluble ("instant") coffee and tea and account for 10% of the total daily intake. The total body content average human adult has about 15 mg of manganese, typically seen in nucleic acid. Daily requirement is about 2-5 mg/day. Manganese acts as an activator of enzyme and as a component of metalloenzymes. They have a role to play in **oxidative phosphorylation, fatty acids and cholesterol metabolism, mucopolysaccharide metabolism, and urea cycle.**

Zinc (Zn): The metal zinc is an omnipotent metal that has amphoteric nature. Hence, it is ionized either in acidic or alkaline forms. Content of zinc is 2-3 ng the average body content of zinc is 2-3 g in an average adult. About 99% is intracellular while the rest is in plasma. The average daily requirement is 15-20 mg/day. Phytase decreases fibers, phosphates, calcium, and copper competes with zinc for absorption from small intestine. About 2-5 mg/day is excreted via pancreas and intestine. The other mode of excretion is via proximal tubule and sweat glands.

Fluorine (F): Fluorine is a lightest element; fluorine plays an important role in the hard tissues of the body such as bone and teeth. It helps in producing denser bones and fluoride has been suggested as a therapeutic agent in the treatment of osteoporosis. It is thought that fluoride, in conjunction with calcium, stimulates osteoblastic activity.

Copper (Cu^{++}): Copper plays a very important role in our metabolism largely because it allows many critical enzymes to function properly. Acidic conditions promote the solubility which incorporates copper ions either in cupric form or cuprous form into the food chain. Mainly copper is available in the liver, shellfish, dried fruit, milk and milk products, sunflower seeds, sesame seeds, tahini, and sun-dried tomatoes. The average adult human of 70 kg weight contains about 100 mg. The daily requirement is about 2-5 mg of which 50% is absorbed from the gastrointestinal tract (GIT).

Iron (Fe): Iron is an essential constituent of **haemoglobin and certain enzymes such as cytochrome oxidase, catalase and peroxidase**. It performs two important functions in the body—to transport oxygen to tissues (through Hb) and to take part in oxidation-reduction reactions (cytochrome system).

Sources: meat, liver, eggs, spinach and fruits.

Absorption: Dietary intake of iron is mainly in ferric (Fe^{+++}) form as hydroxides or in organic compounds. The action of gastric HCl and of some organic acids liberates free ferric ions, which in turn are reduced to ferrous ions (Fe^{++}) by reducing substances such as cysteine or ascorbic acid. The ferrous form of iron is more soluble and thus easily absorbed. The absorption of iron occurs in duodenum and stomach.

Transport and storage: Iron is transported in plasma in ferric form, which remains firmly bound to a specific β-globulin, transferring. The normal concentration of protein bound iron in plasma is 50 - 180μ gm/ 100ml. Iron is stored chiefly in mucosal cells of intestine, liver, spleen and bone marrow as ferritin.

Daily requirement:

Infants – 6–15 mg, Children- 10–18 mg, Adult (male) 10 mg, female- 18 mg.

Posttest

List the basic compounds that iron is an essential component of its formation in the body.

Title:

L 5&6 Blood Gasses

Name of the instructor:

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Target population:

Students of the third stage of medical laboratories

Introduction:

Normal cell metabolism depends on the maintenance of blood pH within very narrow limits (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.

Pretest: **القبلي الاختبار:**

Define pH.

Scientific Content: **المحتوى العلمي:**

Blood Gasses

Blood pH & blood buffer

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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 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 although in clinical medicine the term alkalosis is, perhaps confusingly, reserved for blood pH greater than 7.45 and the term acidosis is reserved for blood pH less than 7.35.

What is a buffer?

A buffer is a solution of a weak acid and its conjugate base.
– The bicarbonate (HCO_3^-) buffer system

Buffers are chemicals in solution which minimize the change in pH which occurs when acids are added by hydrogen ions. In blood, the principal buffer system is the weak acid, carbonic acid (H_2CO_3) and its conjugate base, bicarbonate (HCO_3^-).

Acid -base balance

physiology of acid-base balance: In fact, the lungs ensure removal of carbonic acid (as carbon dioxide) 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
$H^+ + HCO_3^- \leftrightarrow H_2CO_3D \leftrightarrow H_2O + CO_2$
It is important to note that the reactions are reversible. Direction is dependent on the relative concentration of each element. So that, for example, a rise in carbon dioxide concentration forces 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 isexcreted, the lungs regulate the carbon dioxide content of blood. Carbon dioxide diffuses out of tissuecells 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 ofhydrogen 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 bloodplasma.

$$CO_2 + H_2O + \xleftrightarrow{\text{slow}} H_2CO_3 \xleftrightarrow{\text{fast}} H^+ + HCO_3^- \qquad (8\text{-}1)$$

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 rises, 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**.

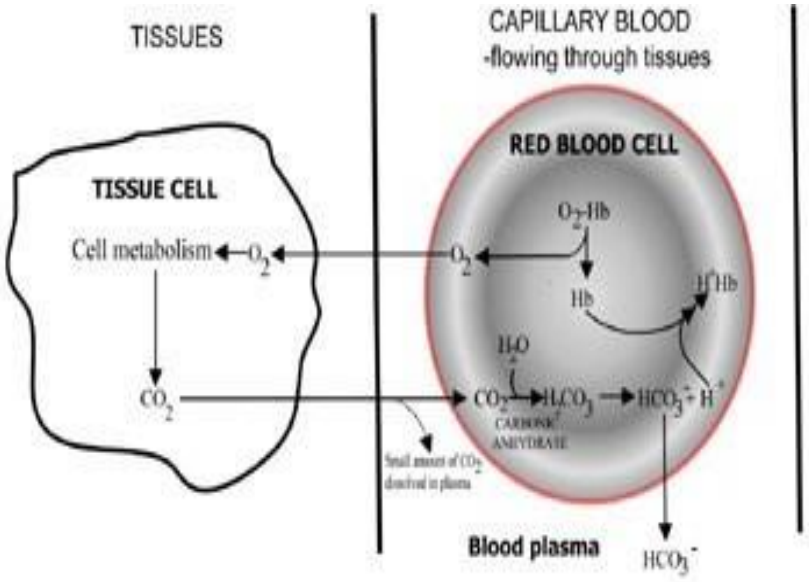


Fig. 1a. CO2 produced in tissues converted to bicarbonate for transport to lungs.

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.

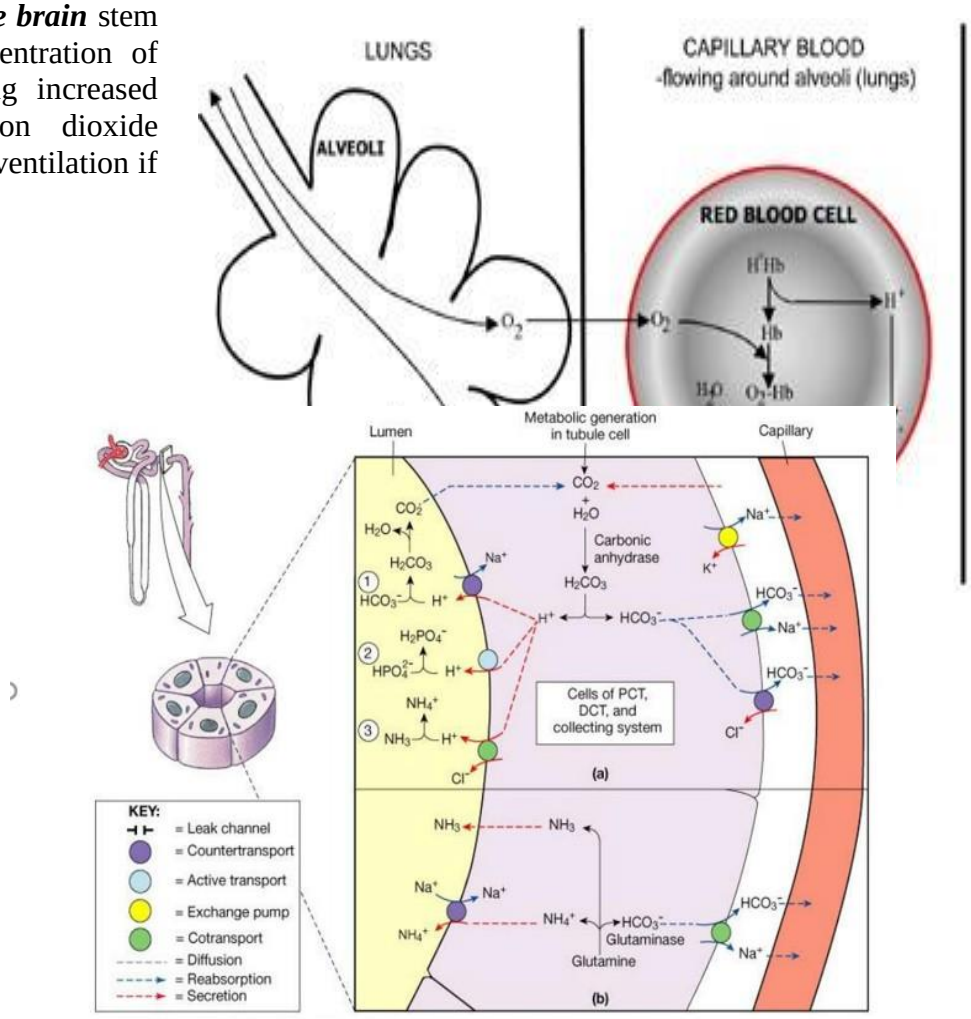


Fig. 1b. At the lungs bicarbonate converted back to CO_2 and eliminated by the lungs.

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 carbonicanhydrase***, which facilitates formation of carbonic acid from carbon dioxide and 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.

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

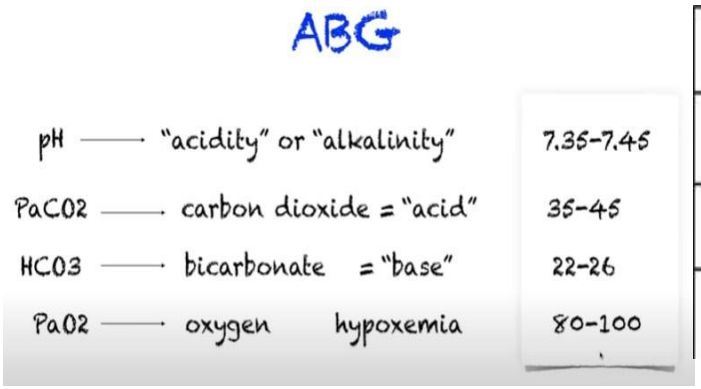
• medical intervention (e.g. mechanical ventilation, some drugs)

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 (pCO2), concentration of bicarbonate (HCO_3^-) are of crucial importance.

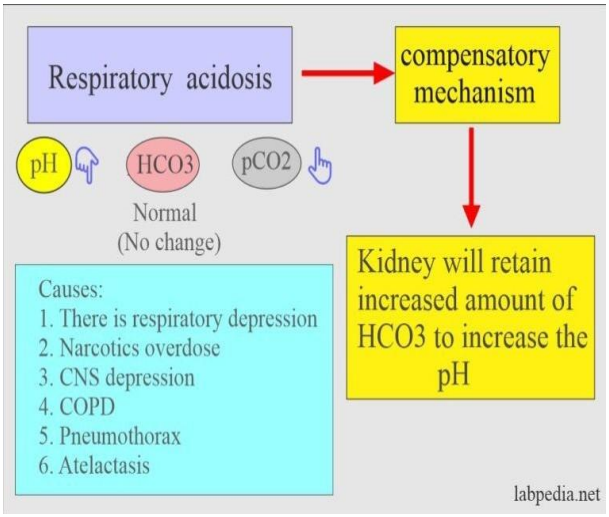
Results of these three allow classification of acid-base disturbance to one of four etiological categories:

Respiratory acidosis – (raised pCO_2, reduced pH)



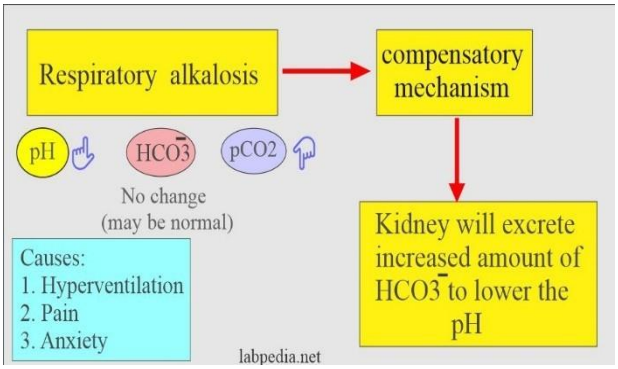
pH	$PaCO_2$	HCO_3
7.35 to 7.45	35 to 45	22 to 26
↑ Acidosis	↓ CO_2 = pH ↑	↓ HCO_3 = pH ↓
↓ Alkalosis	↑ CO_2 = pH ↓	↑ HCO_3 = pH ↑

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**.



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 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

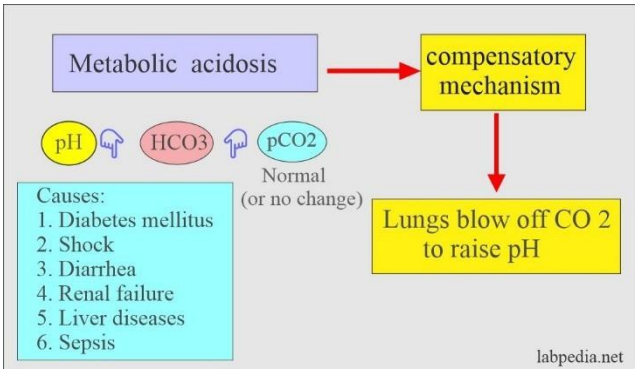


overdose. Primary disturbances of pCO_2 (respiratory acidosis and alkalosis) are compensated for by renal adjustments of hydrogen ion excretion which result in changes in $[HCO_3^-]$ that compensate appropriately for primary change in pCO_2. Thus, the renal compensation for respiratory acidosis (raised 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.

- 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 $[HCO_3^-]$: $pCO2$ returns towards normal.

This occurs for one of two reasons: increased use of bicarbonate in buffering an abnormal acid load or losses of bicarbonate from the body. **Diabetic ketoacidosis and lactic acidosis** are two conditions characterized by overproduction of metabolic acids consequent exhaustion of bicarbonate.



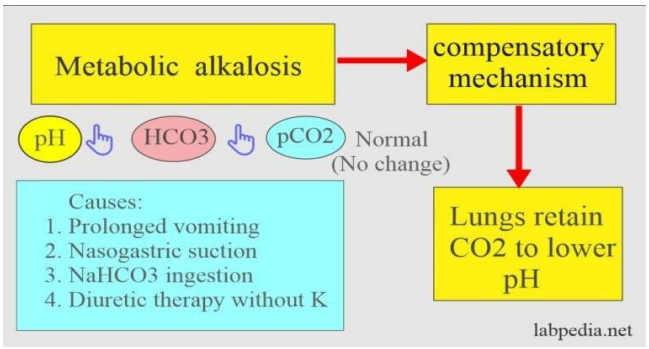
In the first case, abnormally high blood concentrations of keto-acids (**b-hydroxybutyric acid acetoacetic acid**) reflect the severe metabolic derangements which result from **insulin deficiency**.

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**.

Metabolic alkalosis – (increased HCO_3^-, increased pH)

Bicarbonate is always raised in metabolic alkalosis. Compensation for metabolic alkalosis in which $[HCO_3^-]$ is high, by contrast, involves depression of respiration and thereby retention of carbon dioxide so 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.

Acid-base disturbance	pH (N 7.35-7.45)	$PaCO_2$ (N 33-45 mm Hg)	$[HCO_3^-]$ (N 22-28 mmol/L)	Primary	Compensatory
Respiratory acidosis	↓	↑	↑	↑ $PaCO_2$	↑ $[HCO_3^-]$
Respiratory alkalosis	↑	↓	↓	↓ $PaCO_2$	↓ $[HCO_3^-]$
Metabolic alkalosis	↑	↑	↑	↑ $[HCO_3^-]$	↑ $PaCO_2$
Metabolic acidosis	↓	↓	↓	↓ $[HCO_3^-]$	↓ $PaCO_2$

Posttest:

What are the characteristics of respiratory acidosis?

References:

Biochemistry (with Clinical Concepts & Case Studies) .Dr. U. Satyanarayana, Dr. U. Chakrapani

Title:

L7&8 (Diabetes mellitus)

Name of the instructor:

Assist.prof.Dr. Huda farhan ahmed

Target population:

Students of the third stage of medical laboratories

Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels, due to defects in either insulin secretion or insulin action in the body. Diabetes develops due to a diminished production of insulin (**type 1**) or a resistance to its effects (**type 2**), including **gestational diabetes**.

Pretest:

What are the signs of diabetes?

Scientific Content:

Diabetes mellitus

Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels, due to defects in either insulin secretion or insulin action in the body. Diabetes develops due to a diminished production of insulin (**type 1**) or a resistance to its effects (**type 2**), including **gestational diabetes**. This can lead to hyperglycemia, which is largely responsible for the acute signs of diabetes, namely:

• Excessive urine production (polyuria)
• Thirst and increased fluid intake (polydipsia)
• Blurred vision
• weight loss (in type 1)
• Lethargy
• Changes in energy metabolism.

Types of diabetes mellitus:

1- Genetic defects of b-cell function

● Maturity-onset diabetes of the young (MODY):
– MODY 1: mutation of the hepatocyte nuclear factor (HNF4A) gene,
– MODY 2: mutation of the glucokinase gene,
– MODY 3: mutation of the HNF1A gene.
Some cases are thought to be point mutations in mitochondrial deoxyribonucleic acid (DNA) associated with diabetes mellitus and deafness and are usually autosomal dominant.
● Type A insulin resistance (insulin receptor defect).

2- defects of insulin action receptor (insulin resistance (type 2)

3-Insulin deficiency due to pancreatic disease

● Chronic pancreatitis.
● Pancreatectomy.

4-Drugs

- Interferon-a.
- Glucocorticoids.

5-Infections

- Septicemia.
- Congenital rubella.
- Cytomegalovirus. Rare forms of autoimmune-mediated diabetes
- Anti-insulin receptor antibodies.

6-Genetic syndromes associated with diabetes

- Down's syndrome.
- Turner's syndrome.
- Klinefelter's syndrome.

7-Gestational diabetes mellitus

Resembles type 2 diabetes, but is transient, occurring in about 2–5% of pregnancies. While it is fully treatable, about 20–50% of affected women develop type 2 diabetes later in life. Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level at or above 126 mg/dl (7.0 mmol/l).
- Plasma glucose at or above 200 mg/dl (11.1 mmol/l), 2 hours after a 75 g oral glucose load in a glucose tolerance test.
- symptoms of hyperglycemia and casual plasma glucose at or above 200 mg/dl (11.1 mmol/l).

Type 1 diabetes:

The cause of type 1 diabetes is not fully understood. An autoimmune attack (to the β- cells of the pancreas) may be triggered by reaction to an infection, for example by one of the viruses of the Coxsackie virus family or German measles, although the evidence is inconclusive.

Individuals may display genetically; an observed inherited tendency to develop type 1 diabetes has been traced to particular human leukocyte antigen (HLA) genotypes (the major histocompatibility complex (MHC) in humans is known as the HLA system). Environmental factors can also strongly influence expression of type 1 diabetes.

Type 1 diabetes is a polygenic disease (different genes contribute to its expression); it can be dominant, recessive or intermediate. The gene IDDM1, located in the MHC class II region on chromosome 6, is believed to be responsible for the histocompatibility disorder characteristic of type 1 diabetes. Insulin-producing pancreas cells (β-cells) display improper antigens to T-cells, which lead to the production of antibodies that attack those β-cells. Other associated genes are located on chromosomes 11 and 18. Pancreatic β-cells in the islets of Langerhans are destroyed or damaged sufficiently to effectively abolish endogenous insulin production. This an etiology distinguishes type 1 origin from type 2; that is, whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1).

Type 1 diabetes, formerly known as 'childhood', 'juvenile' or 'insulin-dependent' diabetes, is not exclusively a childhood problem. Type 1 diabetes is treated with insulin replacement therapy, usually by insulin injection or insulin pump, along with attention to dietary management and careful monitoring of blood glucose levels.

The most definitive laboratory test to distinguish type 1 from type 2 diabetes is the C-peptide assay, which is a measure of endogenous insulin production. With type 2 diabetes, proinsulin can be split into insulin and C-peptide; lack of C-peptide indicates type 1 diabetes. The presence of anti-islet antibodies or absence of insulin resistance (determined by a glucose tolerance test) is also suggestive of type 1.

Homeostasis Model Assessment (HOMA) =F1* FG /405

Type 2 diabetes

Type 2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic disorder characterized of two processes: a slowly developing resistance to insulin signaling and a compensatory increase in β-cell release of the hormone. With time β-cells no longer produce enough insulin to maintain control of metabolism and type 2 diabetes results.

While the underlying cause of insulin resistance is unknown, there is see correlation between obesity, increased plasma lipids and resistance. Insulin resistance is generally 'post receptor', meaning it is a problem with the cells that respond to insulin rather than a problem with production of insulin. Central obesity (fat concentrated around the waist in relation to abdominal organs, but not subcutaneous fat) is known to predispose individuals to insulin resistance. Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines, which may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes.

There is also a strong inheritable genetic connection in type 2 diabetes. Having relatives (especially first degree) with this disorder substantially increases the risk of developing type 2 diabetes. Environmental exposures may contribute to recent increases in the rate of type 2 diabetes.

A comparison and explanation of the common symptoms of types 1 and 2 diabetes

Symptom	Type 1 diabetes	Type 2 diabetes
Tiredness	Inefficient utilisation of fuels	Inefficient utilisation of fuels
Thirst/polyuria	High glucose (osmotic diuresis)	–
Very low insulin	Damage to insulin-producing β-cells	–
Raised insulin	–	Suggests insulin resistance – linked with obesity
Weight loss	Protein catabolism to provide amino acids for gluconeogenesis, and utilisation of fats for energy	–
Raised HbA1c	High – blood glucose constantly high	Moderate – blood glucose often higher than normal
Ketonuria	Increased metabolism of fats, raised acetyl CoA and increased ketogenesis	–

Glycation

Many of the pathological effects of diabetes arise from the process of glycation. Glycation is the non-enzymatic and haphazard condensation of the aldehyde and ketone groups in sugars with amino groups in proteins, leading to their functional impairment (the enzyme-controlled addition of sugars to protein or lipid molecules is termed

glycosylation). These may undergo further chemical reactions to produce ‘advanced glycation end products’, or (AGEs). Glycation damages collagen in blood vessel walls, leading to inflammation and atherosclerosis. This process is now considered to be a major contributor to diabetic pathology and has resulted in greater clinical emphasis on good glycaemic control. Clinical measurement of glycated haemoglobin (HbA1c) and serum albumin is used to assess the adequacy of blood sugar regulation in diabetic patients (see in table). Normal (non-diabetic) values of glycated haemoglobin are 4.0–6.5%; that is, approximately 6 red cells out of every 100 will have glucose attached.

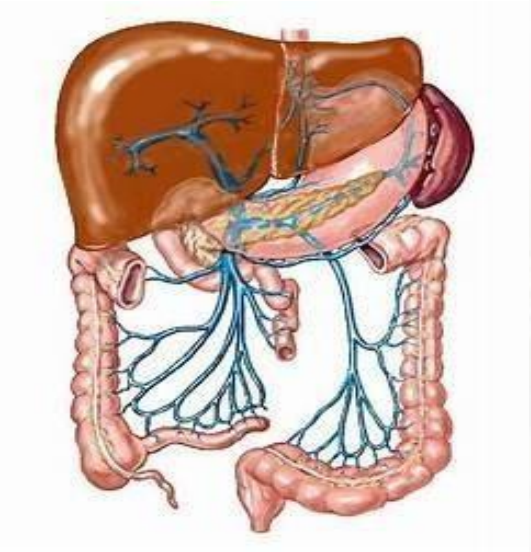
Clinical HbA1c level

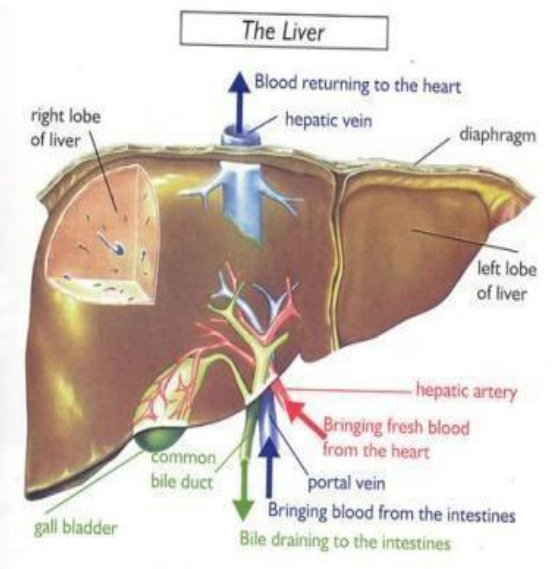
HbA1c (%)	Normal/abnormal	Average blood glucose (mM)
4–6.5	Normal (without diabetes)	3–8
6.5–7.5	Target range (with diabetes)	8–10
8–9.5	High	11–14
>9.5	Very high	>15

Liver Functions and Liver Functions Tests
Lectures 11

Liver:

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





Liver

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

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

Bilirubin

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

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

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

Jaundice

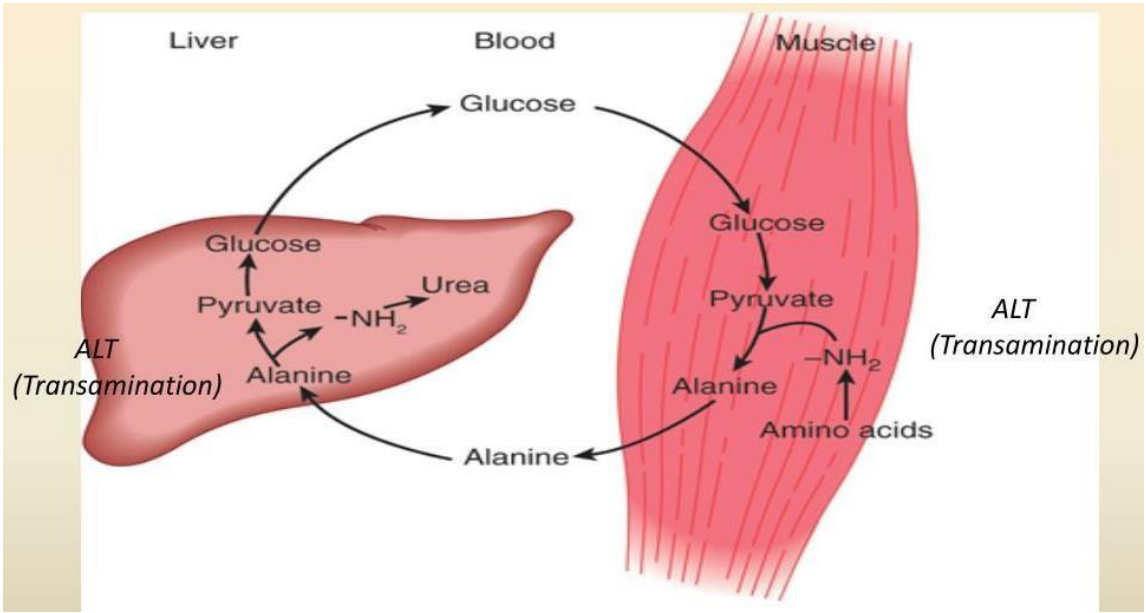
Jaundice is a clinical term referring to yellowing of body tissues due to deposition of bilirubin. Because bilirubin has a high affinity for the sclera of the eye, the most sensitive indicator of Jaundice is yellowing of the sclera, termed scleral icterus, which occurs when plasma bilirubin levels are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

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

Protein Metabolism – Nitrogen Metabolism and The Urea Cycle:

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

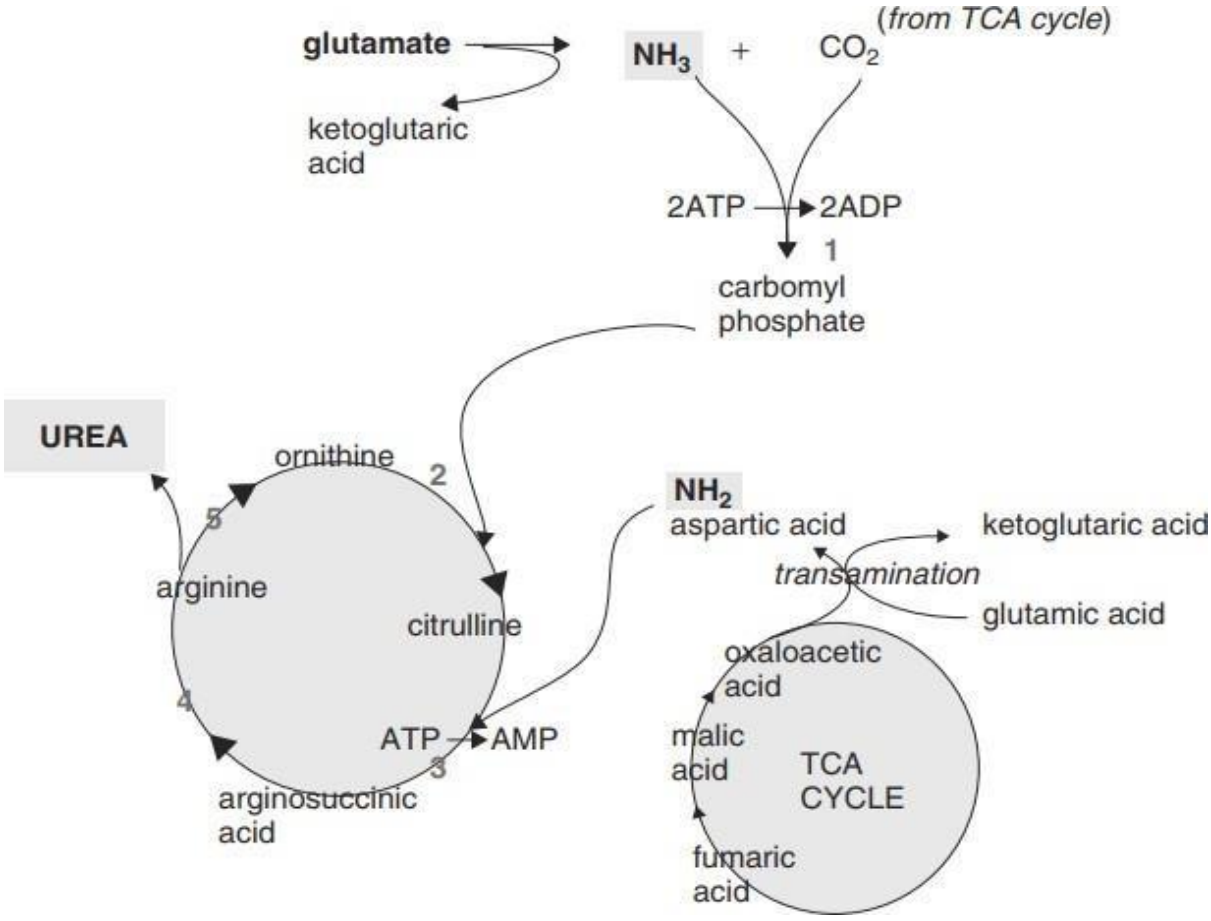
There are specific aminotransferases for all amino acids, except threonine and lysine, and they are particularly abundant in the liver. Alanine transaminase (ALT) and aspartate transaminase (AST) are used as clinical markers of tissue damage. ALT has an important function in the delivery of skeletal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



The urea cycle:

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

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



of nitrogen that must be excreted.

Cirrhosis of the liver

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

LIVER FUNCTION TESTS

1. Write a short note on liver function tests.

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

Functions of liver:

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

Liver function tests are used to:

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

Table 1:(liver function tests).

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

Table 2:(important liver function tests).

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

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

Table 3:(other tests with uses).

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

↑ = increased; ↓ = decreased

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

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

Classification:

Jaundice is classified into three major types:

i. **Prehepatic (hemolytic):** Due to excessive hemolysis, bilirubin production exceeds the capacity of liver toconjugate it.
ii. **Hepatic:** Impaired uptake, conjugation or excretion of bilirubin.
iii. **Postherpetic (obstructive):** Caused by an obstruction in the biliary tract (Table 4).

Table 4: (Classification and findings in jaundice)

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

↑ = increased; ↓ = decreased

3. **Congenital hyperbilirubinemia.**

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

Renal Functions and Renal Functions Tests

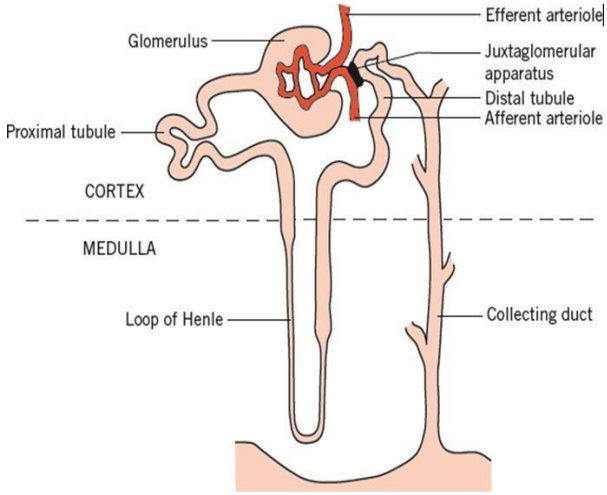
Lecturers 12, 13,14

Kidney:

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

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

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



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

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

RENAL TUBULAR FUNCTION

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

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

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

Clinical and biochemical features of renal disease

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

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

Plasma

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

Urine

- Reduced volume (oliguria).
- Low (appropriate) sodium concentration – only if renal blood flow is low, stimulating aldosterone secretion.

-High (appropriate) urea concentration and therefore a high osmolality – only if ADH secretion is stimulated.

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

Plasma

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

Due to proximal or distal tubular failure:

- low bicarbonate concentration and low pH,
- hypokalaemia.

Due to proximal tubular failure:

- hypophosphataemia, hypomagnesaemia and hypouricaemia.

Urine

Due to proximal and/or distal tubular failure:

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

Due to proximal tubular failure:

- generalized amino aciduria,
- phosphaturia,
- glycosuria.

Acute kidney injury

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

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

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

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

2- Acute oliguria due to intrinsic renal damage

This may be due to:

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

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

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

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

Chronic kidney disease

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

NEPHROTIC SYNDROME

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

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

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

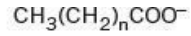
Disorders of Lipid Metabolism

Lectures 14, 15

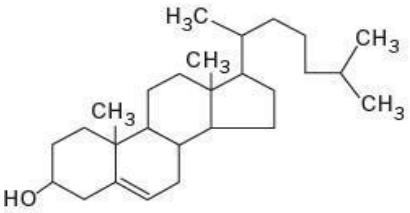
Lipids are defined as organic compounds that are poorly soluble in water but miscible in organic solvents. Lipids play a critical role in almost all aspects of biological life – they are structural components in cells and are involved in metabolic and hormonal pathways. The importance of having a knowledge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

PLASMA LIPIDS

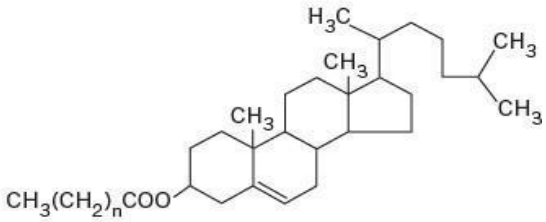
The chemical structures of the four main forms of lipid present



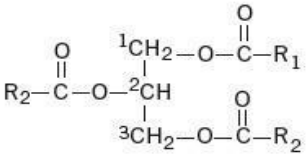
FATTY ACID



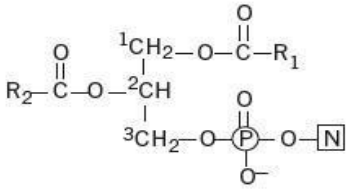
CHOLESTEROL



CHOLESTEROL ESTER



TRIGLYCERIDE



PHOSPHOLIPID

FATTY ACIDS

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

TRIGLYSERID

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

PHOSPHOLIPIDS

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

CHOLESTEROL

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

LIPOPROTEINS

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

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

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

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

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

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

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

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

Clinical significance of lipid fractionation:

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

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

classification there are 5 types of hyperlipoproteinemia

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

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

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

and cholesterol level increases.

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

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

f) Type V hyperlipoproteinemia: Increase in VLDL & chylomicron

II) Hypolipoproteinemia:

Condition of decreased lipoprotein fraction is termed as hypolipoproteinemia.

a) Familial hypolipoprotenemia:

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

b) Abeta lipoprotenemia:

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

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

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

Cholesterol

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

Hypercholesterolemia and development of atherosclerosis and CHD:

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

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

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

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

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

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

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

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

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

Heart Functions and Heart Functions Tests
Lectures 16, 17

Heart Diseases include:

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

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

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

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

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

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

blockage of blood flow through these coronary arteries ischemia.

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

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

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

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

1. Lactate dehydrogenase isoenzymes:

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

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

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

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

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

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

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

Pancreatic Functions and Pancreatic Functions Tests

Lectures 18

Pancreas:

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

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

The digestive enzymes

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

Tests of pancreatic function

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

Fecal Fat Analysis

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

Blood Proteins
Lectures 19 and 20

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

How is blood plasma different from serum

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

Total Protein

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

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

What are the functions of proteins:

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

What are some of the functions of Albumin?

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

equilibrium betweenplasma and interstitial fluidis seen clinically as edema

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

Globulin

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

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

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

α- globulin:

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

β- globulin:

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

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

γ –region Globulin:

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

References:

1. Clinical chemistry in diagnosis and treatment , Joan F .Zilva , 5th Edition 1989.
2. Fundamentals of clinical chemistry , Norbert W. Tiets , 2nd Edition 1982 . Harper's Biochemistry , R . K . Murry , D . K . Garnner , P . A . Mays and V . W . Rodweu , 21 Edition , 1988.

ENZYMES

- **Functional plasma enzymes**: Present in plasma at a higher concentration than in tissues.

1- Mostly synthesized by the liver

2- Usually decreased in disease conditions (E. g. Clotting enzymes)

- **Non-functional plasma enzymes:**
  1-Present in plasma at a lower concentration than tissues
  2-Do does not have any function in the plasma
  3-Mostly synthesized by the liver, skeletal muscle, heart, brain

Usually increased in disease conditions (E. g. Creatine kinase, Alanine transaminase)

- **Assessment of Cell Damage and Proliferation**

Plasma enzyme activities can be used in the diagnosis of disease and the prognosis of treatment. Plasma enzyme levels depend on the balance between the rate of influx of active enzyme into the circulation and its eventual clearance from the blood.

- **Estimation of more than one enzyme**

Many enzymes are widely distributed, but their relative concentrations may vary in different tissues. For Ex., Alanine and aspartate transaminases (GOT&GPT) are

abundant in the liver, and the concentration of aspartate transaminase (GOT) is much greater than that of alanine transaminase (GPT) in heart muscle

- **Isoenzyme's determination**

Some enzymes exist in more than one form: these isoenzymes may be separated by their different physical or chemical properties.

a-Amylase: Marked increase (five to 10 times the upper reference limit): Acute pancreatitis, Severe glomerular impairment

Moderate increase (up to five times the upper reference limit): Perforated peptic ulcer, Acute cholecystitis, Intestinal obstruction, Salivary gland disorders like mumps, salivary calculi

Lipase

Plasma lipase levels are elevated in acute pancreatitis and carcinoma of the pancreas. Clinical Significance

Serum **amylase** is increased in mumps, pancreatic disease, or due to some other cause, whereas **lipase** is increased only in pancreatitis. Therefore, the determination of both amylase and lipase together helps in the diagnosis of acute pancreatitis

Trypsin

• Trypsin: (TRY): is a serine proteinase that hydrolyzes the peptide bonds formed by the carboxyl groups of lysine arginine with other amino acids. Increased in pancreatic disease.

- **Liver enzymes:**

  There are three types of enzymes:

  1. Enzymes that are normally present inside the hepatocytes are released into the blood when there is hepatocellular damage = markers of hepatocellular damage.

  2. Enzymes that are primary membrane-bound (plasma membrane or side of hepatocytes) = markers of cholestasis

  3. Enzymes that are synthesized in the hepatocyte = indicate disturbances in the hepatocellular synthesis

Markers of hepatocellular damage:

1. Aminotransferases/Transaminases (GPT): Elevated plasma GPT is considered to be relatively specific for liver disease

• GOT may be elevated in other forms of tissue damage, such as myocardial infarction, muscle necrosis, and renal disorders.

Markers of cholestasis:

1. Alkaline phosphatase (ALP). Half-life= 10 days.

2. Gamma-glutamyl-transferase (glutamyl transferase; GGT): catalyzes the transfer of the–glutamyl group from peptides, GGT occurs mainly in the cells of the liver

Isoenzymes of creatine kinase

• CK consists of two protein subunits, M (for muscle) and B (for the brain), which combine to form three isoenzymes. BB (CK-1), MB (CK-2) and MM (CK-3).

• **CK-MM** is the predominant iso-enzyme in skeletal and cardiac muscle and is

detectable in the plasma of normal subjects.

• **CK-MB** accounts for about 35 percent of the total CK activity in cardiac muscle and less than five percent in skeletal muscle

• **CK-BB** is present in high concentrations in the brain and in the smooth muscle of the gastrointestinal and genital tracts.

Lactate Dehydrogenase

• Lactate Dehydrogenase catalysis the reversible inter-conversion of lactate and pyruvate. The enzyme has high concentrations in cells of cardiac and skeletal muscle, liver, kidney, brain, and erythrocytes.

TUMOR MARKERS

These are biochemical indicators of the presence of a tumor. In clinical practice, it refers to a molecule that can be detected in plasma and body fluids.

Tumor markers are measurable biochemicals that are associated with malignancy. These markers are either produced by tumor cells (tumor-derived) or by the body in response to tumor cells (tumor-associated). They are typically substances that are released into the circulation and thus measured in the blood. Tumor markers are not the primary modalities for cancer diagnosis rather they can be used as a laboratory test to support the diagnosis.

Q/ Why use tumor markers?

Screening and Early Detection of Cancer. Screening refers to looking for cancer in people who have no symptoms of the disease. Some newer tumor markers help to assess how aggressive a cancer is likely to be or even how well it might respond to certain drugs. Cancer Markers are also used to detect cancers that recur after initial treatment. Some tumor markers can be useful once treatment has been completed and with no evidence of residual cancer left.

- **Determining direction**

  Tumor markers can be measured qualitatively or quantitatively by:

  1. Chemical methods.
  2. Immunological methods.
  3. Molecular biological methods to determine the presence of cancer.

  Characteristics of Ideal Tumor Markers

  1. Specificity for cancer: the substance should be produced only by the tumor.
  2. Sensitivity for cancer: a very small tumor growth will produce measurable amounts of the marker.
  3. The amount of marker produced: will correlate well with the tumor load.
  4. The assay for the marker: must be inexpensive, easy to perform, and sensitive.
  5. The half-life of the marker: must be short enough, so
  6. That when production drops, the level falls off rapidly.

- **Classification of Tumor Markers**

  1. Enzymes and isoenzymes.
  2. Hormones, neurotransmitters, and their metabolites.
  3. Receptors (estrogen, progesterone, androgen, and corticosteroid).
  4. Serum proteins examples of (immunoglobulins, glycoproteins, carcinoembryonic proteins, or oncofetal antigens).

HORMONE

➢ Concept of hormones:

Hormones are chemicals that are responsible for controlling and regulating the activities of certain cells and organs. These hormones are secreted by ductless glands known as endocrine glands.

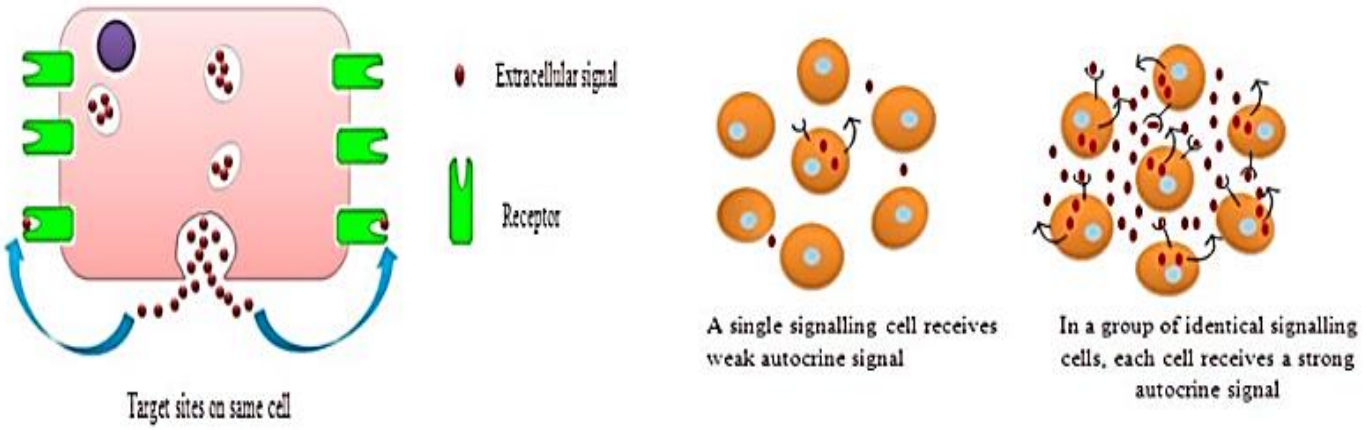
The nervous system and endocrine system are the major control mechanisms that integrate the functions of the tissues in the body. The nervous system transmits electrochemical signals between the brain and peripheral tissues for coordinating diverse body functions.

The endocrine system releases chemical mediators or hormones into circulation. However, both these systems converge, so that neural regulation of endocrine glands is affected.

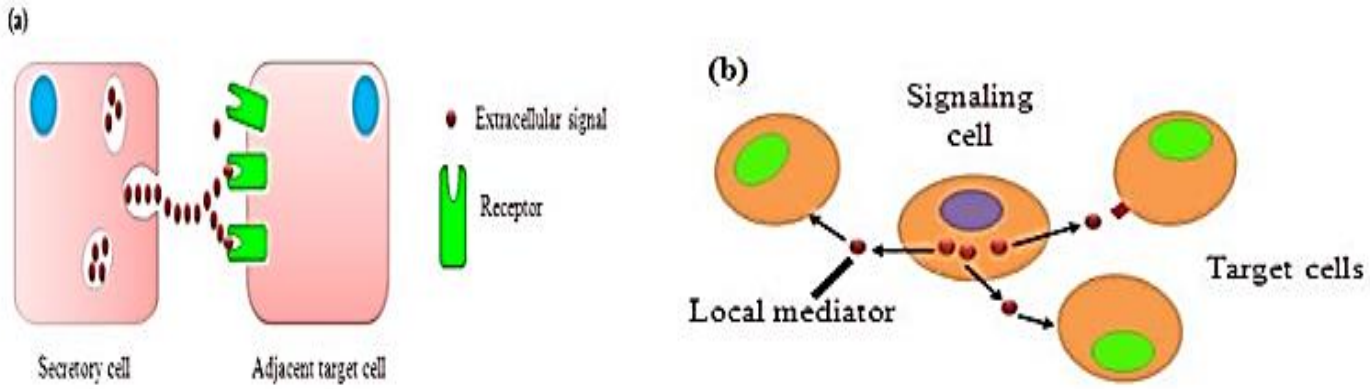
Signal molecules are of different types and the process of transferring the signal into the cell is called signal transduction. There are two types of cells in signal transduction the sender cell where the signal originates and the target cell that receives the signal. The signal alters or modulates the activity/function of the cell. The types of these signals are:

1- Autocrine signaling occurs when the same cell acts as sender and recipient,

e.g., growth.

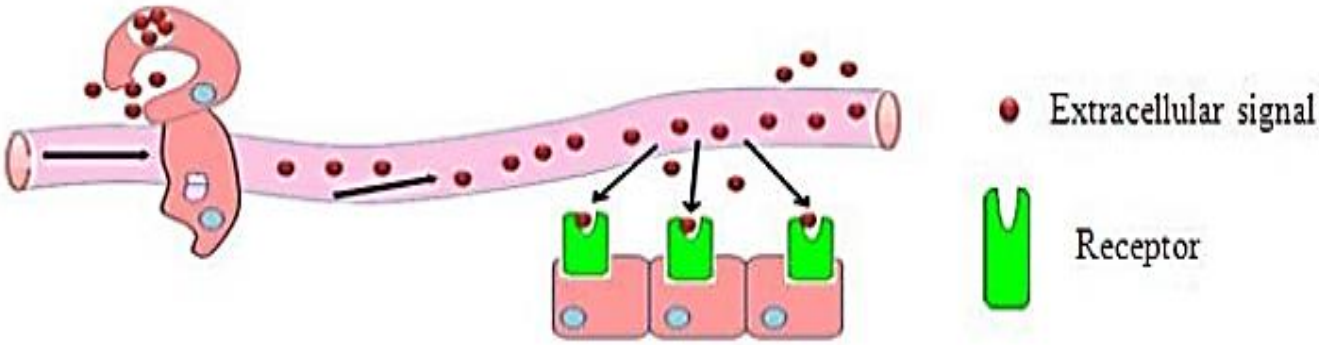


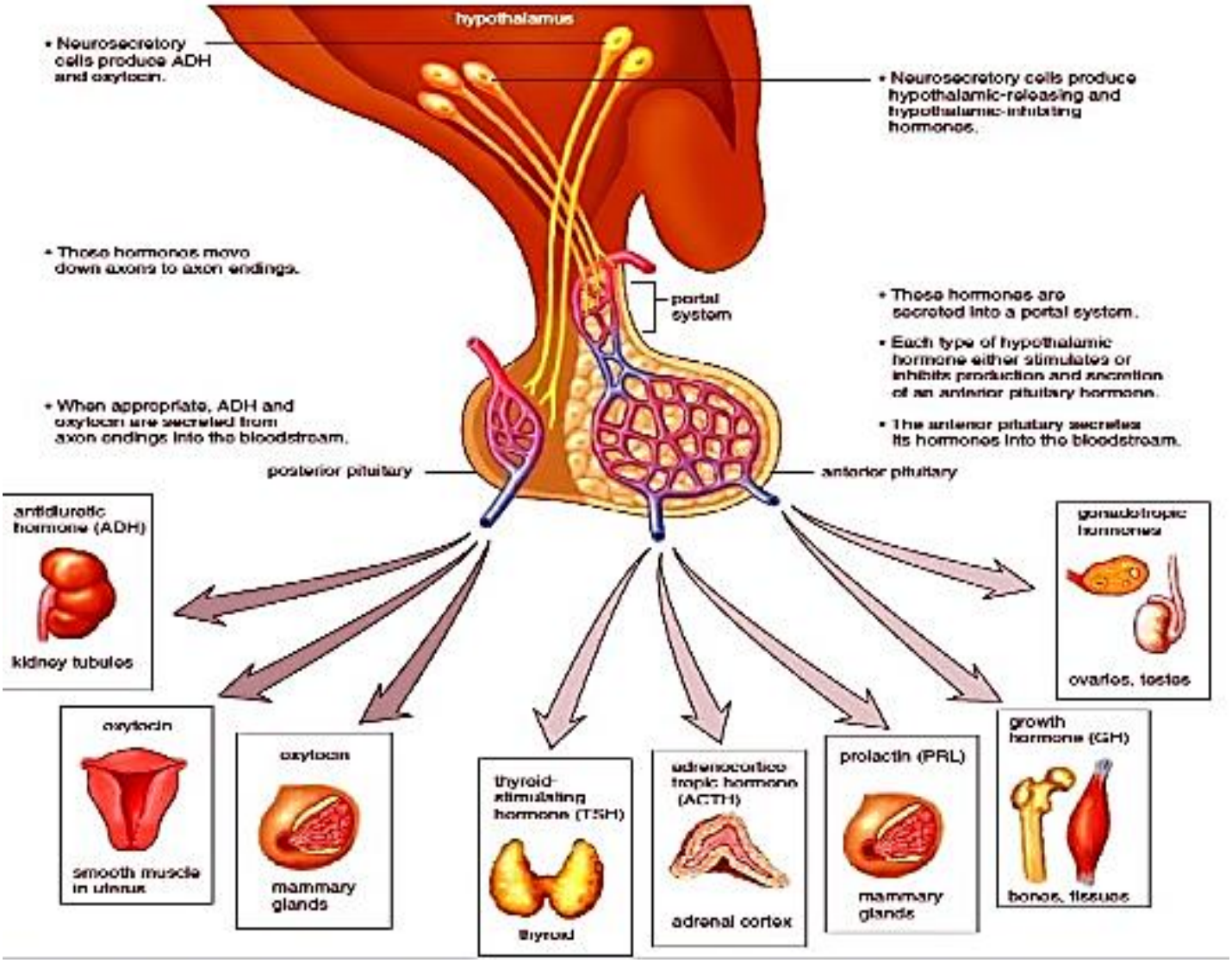
2- Paracrine signaling is affected by local mediators which have their effect near the site of secretion without entering the circulation.



3- Juxtracrine signaling occurs when the two types of cells are adjacent to each other.

4- Endocrine signaling is between cells that are located at a distance from each other and the signal may be hormones or chemical messengers secreted into circulation. Once they reach the target cell, they bind to specific target cell receptors with high affinity.


Extracellular signal
Receptor


hypothalamus
• Neurosecretory cells produce ADH and oxytocin.
• Neurosecretory cells produce hypothalamic-releasing and hypothalamic-inhibiting hormones.
• These hormones move down axons to axon endings.
portal system
• These hormones are secreted into a portal system.
• Each type of hypothalamic hormone either stimulates or inhibits production and secretion of an anterior pituitary hormone.
• The anterior pituitary secretes its hormones into the bloodstream.
• When appropriate, ADH and oxytocin are secreted from axon endings into the bloodstream.
posterior pituitary
anterior pituitary
antidiuretic hormone (ADH)
kidney tubules
gonadotropic hormones
ovaries, testes
oxytocin
smooth muscle in uterus
oxytocin
mammary glands
thyroid-stimulating hormone (TSH)
thyroid
adrenocorticotropic hormone (ACTH)
adrenal cortex
prolactin (PRL)
mammary glands
growth hormone (GH)
bones, tissues

The hypothalamus produces two types of endocrine factors;

a- Hypothalamic neuropeptides. These neurohormones are antidiuretic hormone (ADH) and oxytocin.

b- Hypothalamic releasing: The releasing factors are neurosecretions synthesized in the hypothalamus and released through the hypothalamic-pituitary portal circulation. They have an effect on the secretion of pituitary tropic hormones.

Name	*Chemical nature*	*Biological actions*
TRH; thyrotropin releasing hormone	Tripeptide; (pyro-Glu-His-Pro-NH_2)	Induces secretion of TSH and PRL; neuromodulator
GnRH; gonadotropin releasing hormone	Biologically active portion is a decapeptide	Releases LH and FSH; induces spermatogenesis, ovulation and testosterone
GHRH; growth hormone releasing hormone	37–44 amino acid; amino terminal end is tyrosine	Stimulates growth hormone secretion
CRF; corticotropin releasing factor	Amidated peptide with 41 amino acids	Release of ACTH. Inhibited by cortisol
Somatostatin; growth hormone inhibitory factor	Cyclic peptide with 14 amino acids	Inhibits secretion of GH and TSH. Inhibits gut hormones, pancreatic and gastric secretion
PIF; prolactin inhibitory factor	Dopamine	Inhibits PRL release

Direct connection between hypothalamus & adrenal medulla: it controls epinephrine & norepinephrine secretion.

The pituitary gland is the master gland: The pituitary is a small, pea-sized gland situated at the base of the brain, ant. The pituitary controls 3 endocrine glands: the thyroid,

adrenal glands, and gonads. 3 endocrine glands not controlled by the pituitary; parathyroid, adrenal medulla, and pancreas

Acronym	*Full name*	*Chemical nature*	*Mol.wt. in kD*	*Amino acids*
GH	Growth hormone	Polypeptide	22	191
ACTH	Adrenocortico-tropic hormone	Polypeptide	4.5	39
LH	Luteinizing hormone	Glycoprotein; α,β chains	29	α = 89 β = 115
FSH	Follicle stimulating	Glycoprotein; α,β chains hormone	29	α = 89 β = 115
TSH	Thyroid stimulating hormone	Glycoprotein; α,β chains	28	α = 96 β = 115
MSH	Melanocyte stimulating hormone	Polypeptide	13	α = 13 β = 18 γ = 12
PRL	Prolactin b Endorphins	Polypeptide Polypeptides	22 4	198 31
LPH	Lipotropic hormone	Polypeptide	11	β = 91 γ = 60

Several other glandular tissues are considered to secrete hormones:

Heart: atrial natriuretic peptide (ANP).

kidney: produce the hormone erythropoietin, renin &1,25(OH)2cholecalciferol.

Thymus: This produces a hormone that circulates from this organ to stem cells in the lymphoid organ inducing them to become immunologically competent lymphocytes. **GI tract**: are called GI Hormones.

- **Biochemical structure & synthesis hormones: they are classified as:**

1. Steroid hormones: such as adrenocorticosteroid hormones, and progesterone.
2. Amino acid derivatives: such as epinephrine, norepinephrine and thyroid hormones.
3. Peptide/Protein hormones: such as Insulin, glucagon, parathormone, calcitonin, pituitary hormones,

Chemical structure & synthesis of hormones		
	Water soluble	Lipid soluble
Chemical nature	Protein & polypeptide (most hormones)	Steroid (sex hormones)
Gland	Pituitary, pancreas & parathyroid	Gonads & adrenal cortex
Action	Activation of enzymes	Synthesis of enzymes
Onset	Rapid action (minutes)	Slow action (hours or days)
Site of formation	In rER	In SER from cholesterol
Storge	more	Little
Release	By exocytosis	Carried plasma proteins

The Plasma carrier proteins exist for all classes of endocrine hormones. Carrier proteins for peptide hormones prevent hormone destruction by plasma proteases. Carriers for steroid and thyroid hormones allow these hydrophobic hormones to be

present in the plasma. Carriers for small, hydrophilic amino acid-derived hormones prevent their filtration through the renal glomerulus, greatly prolonging their circulating half-life.

➢ The Character Of Endocrine Hormone:

1- They are secreted directly in blood in small amounts (very active).

2- Some hormones have generalizer action e.g., growth hormone & thyroxine. Others affect specific target organs e.g., sex hormones & ACTH.

3- Hormones are removed either by target cell uptake, metabolism inactivation by the liver, or excretion by the kidney.

4- Hormones play a key role in the regulation of almost all body functions including metabolism, growth, development, H2O and electrolyte balance, reproduction, and behavior.