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

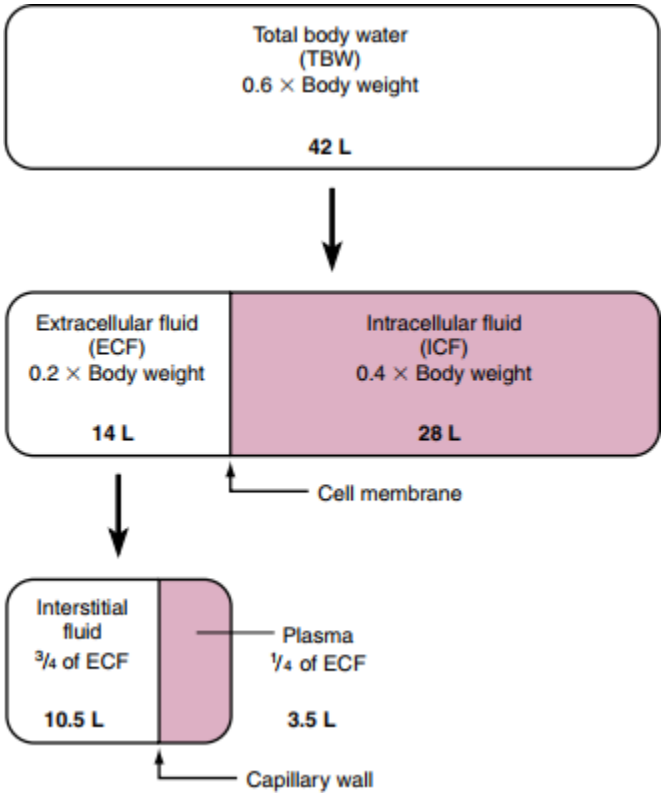
Water is an essential body constituent, and homeostatic processes are important to ensure that the total water balance is maintained within narrow limits, and the distribution of water among the vascular, interstitial and intracellular compartments is maintained.
The body maintains a balance of water 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.

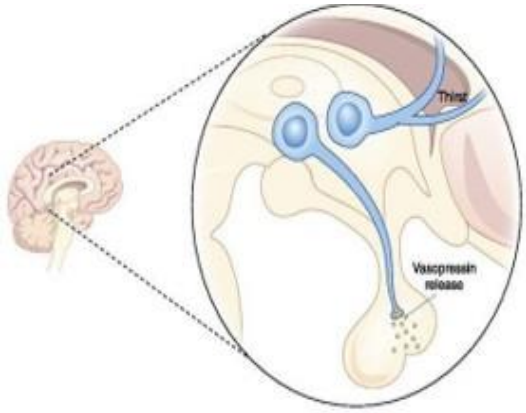
Dehydration: • When water, but not solute, is lost, dehydration occurs. Dehydration involves a loss of volume but, because solutes are not lost in the same proportion, plasma osmolarity increases. Although sweating causes the loss of some solute through the skin, much more water is lost, and the person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

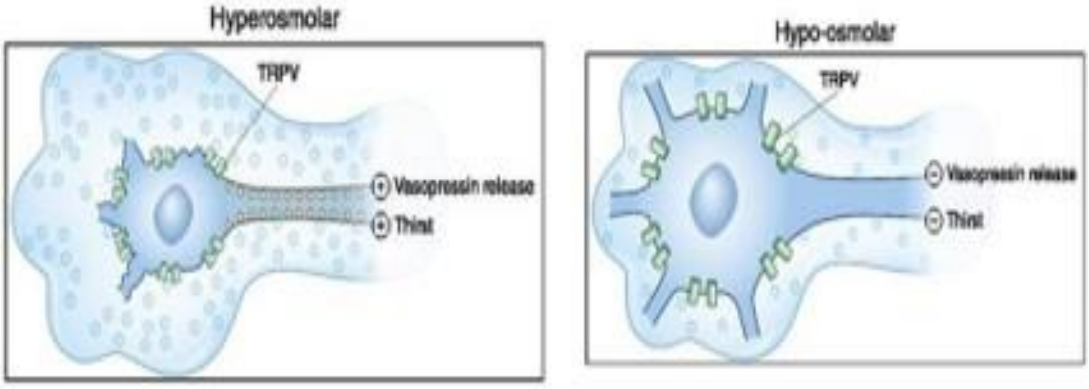
Effect of ADH

• 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

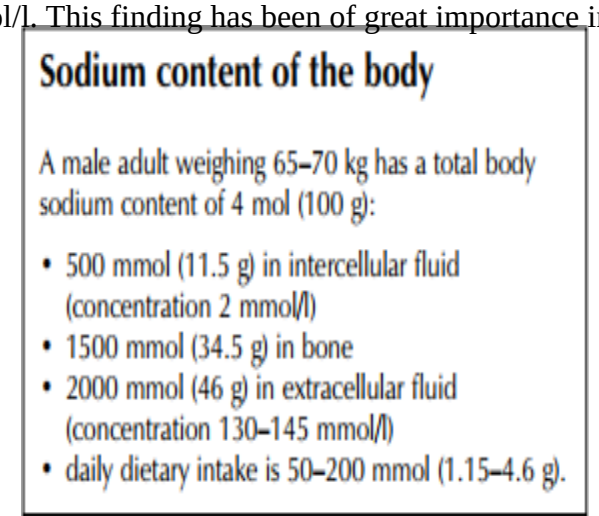
• Quantity elements (electrolytes) — Na (Sodium), Mg (Magnesium), K (Potassium), Ca (Calcium), P (Phosphorus), S (Sulfur), Cl (Chlorine).
• Essential trace elements — Mn (Manganese), Fe (Iron), Co (Cobalt), Ni (Nickel), Cu (Copper), Zn (Zinc), Mo (Molybdenum), Se (Selenium), I (Iodine).
• Function suggested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

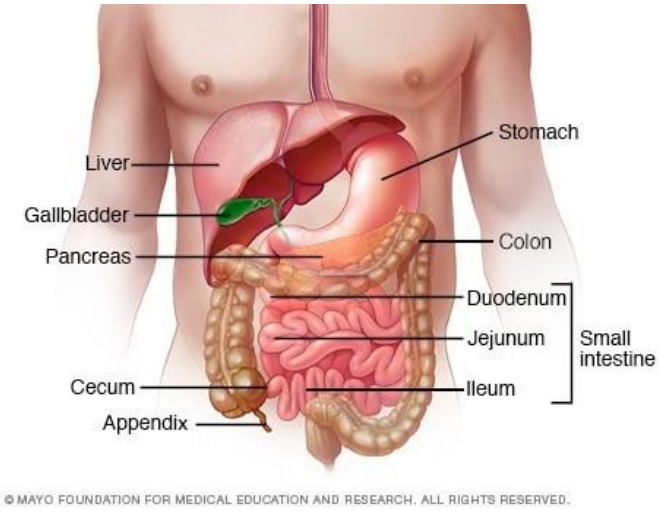
Electrolytes (Na, K, Mg, Ca, Cl)

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:

Assist.prof.Dr. Huda farhan ahmed

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**.

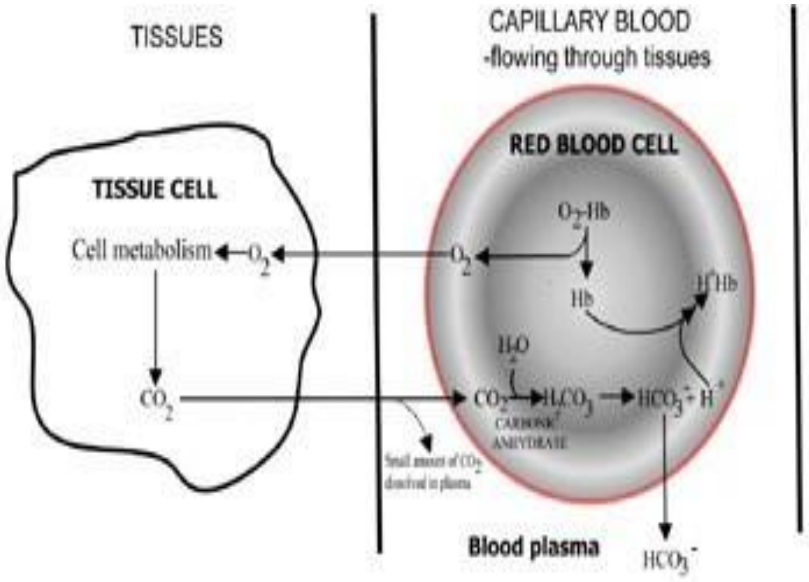


Fig. 1a. CO2 produced in tissues converted to bicarbonate for transport to lungs.

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.

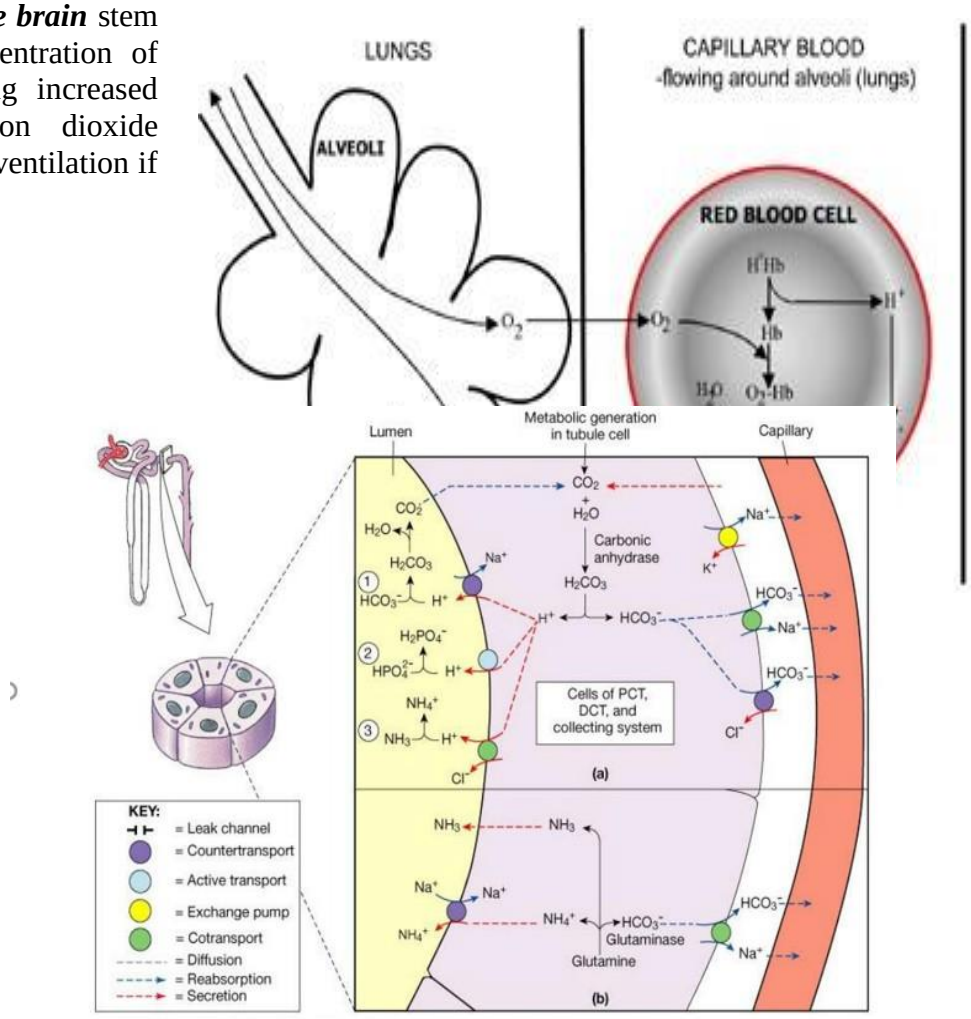


Fig. 1b. At the lungs bicarbonate converted back to CO_2 and eliminated by the lungs.

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

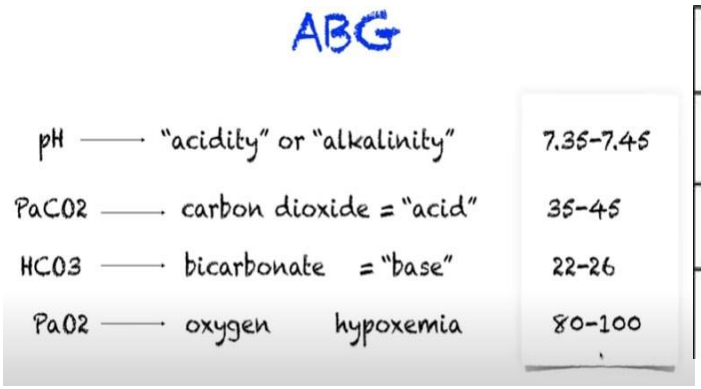
• medical intervention (e.g. mechanical ventilation, some drugs)

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.

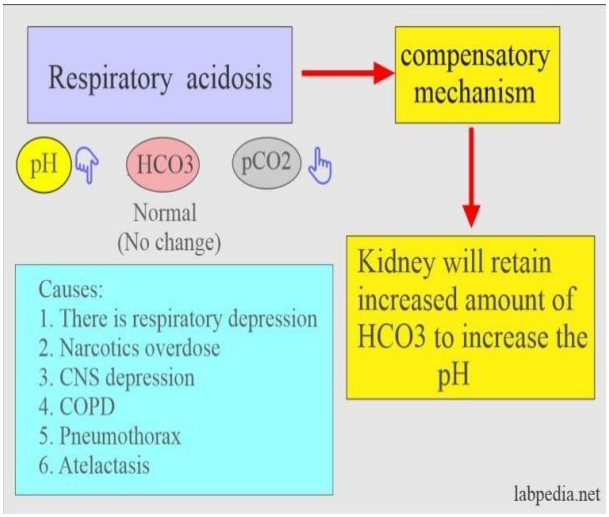
Results of these three allow classification of acid-base disturbance to one of four etiological categories:

Respiratory acidosis – (raised pCO_2, reduced pH)



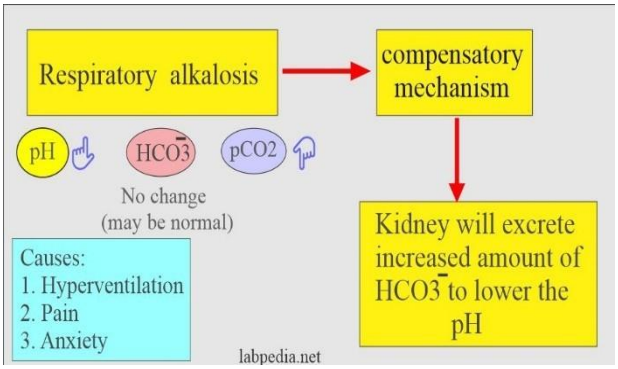
pH	$PaCO_2$	HCO_3
7.35 to 7.45	35 to 45	22 to 26
↑ Acidosis	↓ CO_2 = pH ↑	↓ HCO_3 = pH ↓
↓ Alkalosis	↑ CO_2 = pH ↓	↑ HCO_3 = pH ↑

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

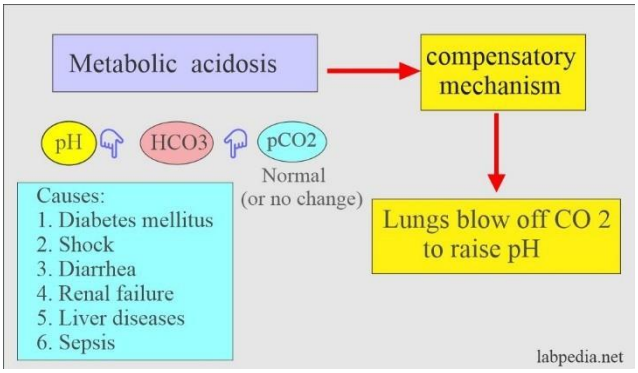


overdose. Primary disturbances of pCO_2 (respiratory acidosis and alkalosis) are compensated for by renal adjustments of hydrogen ion excretion which result in changes in $[HCO_3^-]$ that compensate appropriately for primary change in pCO_2. Thus, the renal compensation for respiratory acidosis (raised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



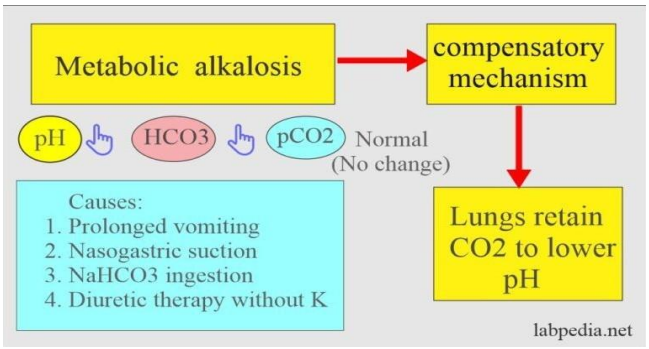
In the first case, abnormally high blood concentrations of keto-acids (**b-hydroxybutyric acid acetoacetic acid**) reflect the severe metabolic derangements which result from **insulin deficiency**.

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