Minerals & Trace Elements

Our diet contains four essential nutrients, these are: vitamins, essential fatty acids, essential amino acids, and minerals.

Minerals are inorganic chemical elements essential for human survival, of no caloric value, and are not degraded by digestion or cooking; deficiency in any of them may lead to serious consequences.

The major six minerals present in the human body in order of abundance are:

calcium, phosphorus, potassium, sodium, chloride, and magnesium. These are called the major elements or macrominerals and their daily requirement is more than 100mg/day.

These six minerals together with non-mineral elements carbon, hydrogen, oxygen, and nitrogen comprise around 99.9% of the human body.

Trace elements are minerals that present in a very minimal concentration in the human body, they include iron, cobalt, copper, zinc, manganese, molybdenum, iodine, and selenium, but the total number of chemical elements that are absolutely needed is not known for any organism. These are also called the minor elements or microminerals and their daily requirement is less than 100mg/day.

Minerals will be discussed briefly in this lecture according to their clinical importance.

I- Calcium metabolism

Calcium is the most abundant mineral in the body, there being about 25 mol (1 kg) in a 70 kg man. Approximately 99% of the body's calcium is present in the bone combined with phosphate, in turn about 85% of the body's phosphate content is in the bone.

Calcium is present in 3 forms:

1- Ionized (free) calcium

2- Protein-bound calcium

3- Calcium complex

Disorders of calcium homeostasis are relatively common biochemical abnormalities that might be the cause or the result of serious medical conditions. The daily requirement varies according to the age where children require 500 mg/day while adults require more than 1000 mg/day.

Calcium homeostasis

In adults, calcium intake and output are normally in balance. Balance is largely achieved through matching net absorption over 24 h closely with the corresponding 24-h urinary excretion; this varies with the diet.

In infancy and childhood, there is normally a positive balance, especially at times of active skeletal growth.

In older age, calcium output may exceed input, and a state of negative balance then exists; this negative external balance is particularly marked in women after menopause and is important in the development of postmenopausal osteoporosis. In women, the mother loses calcium to the fetus during pregnancy, and by lactation.

Function of calcium

1- Calcium is a major mechanical constituent of the bone. Calcium salts in bone have a mechanical role but are not metabolically inert. There is a constant state of turnover in the skeleton associated with deposition of calcium in sites of bone formation and release at sites of bone resorption (~5% per year of the adult skeleton is remodelled). Calcium in the bone also acts as a reservoir that helps to stabilize plasma calcium.

2- Maintenance of extracellular ionized calcium within narrow limits is necessary for normal excitability of nerve and muscle. An increase in ionized calcium raises the threshold for the nerve action potential and vice versa.

3- The ion is also required in the activation of the clotting and complement cascades.

4- It is vital for many enzymes to function properly.

5- It acts as a second messenger for different hormones.

Calcium component	Percentage of plasma [calcium]
Ionised calcium, Ca^{2+}	50–65
Calcium bound to plasma proteins – mainly albumin	30–45
Calcium complexed with citrate, etc.	5–10

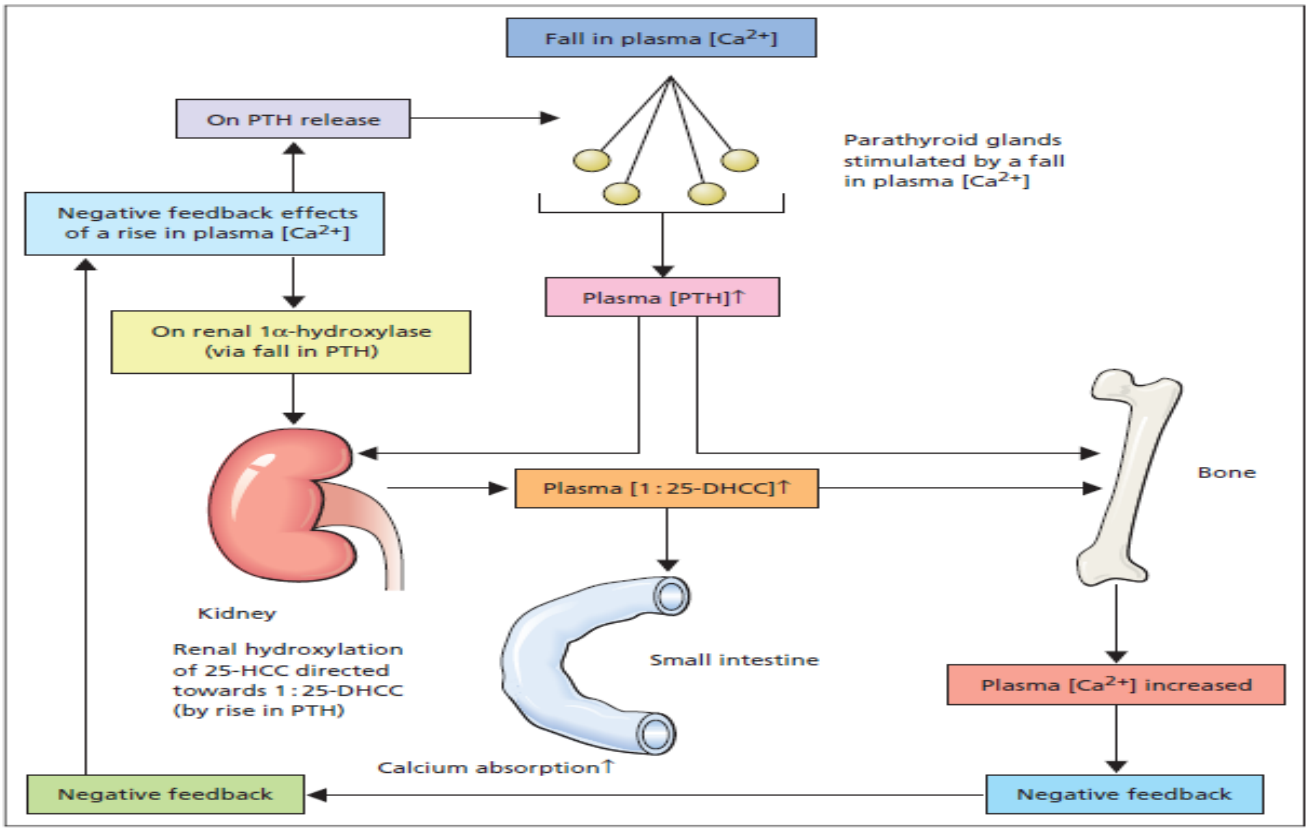
The components of calcium in plasma

Control of calcium metabolism

Calcium is present in plasma in three forms, in equilibrium with one another. Plasma [Ca2+] is the physiologically important component and is closely regulated in humans by PTH and 1:25-dihydroxycholecalciferol: both acts to increase plasma [Ca2+] .

Growth hormone (GH), glucocorticoids (e.g. cortisol), oestrogens, testosterone and thyroid hormones (thyroxine (T4) and tri-iodothyronine (T3)) also influence calcium metabolism.

The body's responses to a fall in plasma [Ca2+] are shown in the following figure.



In case of hypocalcemia, the following response occurs:

1- hypocalcemia stimulate secretion of PTH

2- PTH has two main functions:

A- on the kidneys: stimulates one alpha-hydroxylase, which in turn leads to more hydroxylation of 25(OH)D3 into the active form 1,25 $(OH)_2D3$.

B- on bones: stimulates the release of calcium from bone to blood (bone resorption).

3- the active form of vitamin D will increase calcium absorption at the small intestine, and increase bone resorption as well.

4- hypocalcemia will be corrected by increasing calcium absorption by the action of vitamin D and by the release of calcium from bones by the action of both vitamin D and PTH. Correction of plasma calcium has a negative feedback effect on the parathyroid gland leading to inhibition of PTH.

Effects of plasma H+

In acidosis, the protonation of albumin reduces its ability to bind calcium, leading to an increase in unbound [Ca2+], and vice versa, without any change in total [calcium]. Thus, hyperventilation with respiratory alkalosis can reduce plasma [Ca^{2+}], with the development of tetany. In chronic states of acidosis or alkalosis, PTH acts to readjust the plasma [Ca^{2+}] back to normal. Even within the intestine, acidity favours calcium absorption.

Calcitriol stimulates osteoblasts to secrete alkaline phosphatase. Due to this enzyme, the local concentration of phosphate is increased. The ionic product of calcium and phosphorus increases, leading to mineralization and remodelling of bone.

Calcitriol increases the reabsorption of calcium and phosphorus by renal tubules, therefore both minerals are conserved. (PTH conserves only calcium).

Effects of serum [albumin]

Because albumin is the principal binding protein for calcium, a fall in serum [albumin] will lead to a fall in bound calcium and a decrease in total [calcium] (and vice versa). Under these circumstances, the unbound plasma [Ca^{2+}], the physiologically important fraction, will be maintained at normal levels by PTH. Modest but potentially misleading increases in serum [calcium] may also result from abnormal calcium-binding, due to raised serum [albumin]. For this reason, a corrective equation has been used to avoid this possible misleading result of serum calcium level in case of altered albumin level:

Corrected Ca = serum Ca + [0.08 x (40 – serum albumin)]

Effect of Calcitonin

Calcitonin is a hormone secreted by the thyroid gland responsible for the prevention of bone resorption, hence, decreasing serum calcium level through decreasing the activity of osteoclasts and increases that of osteoblasts. This is why serum calcitonin level increases in case of hypercalcemia and decreases in case of hypocalcemia. As a drug, it is used for the treatment of many bony disorders.

in summary, calcitonin, calcitriol and PTH work together to regulate plasma calcium level.

Comparison of the action of the three major factors affecting serum calcium			
	Vitamin D	*PTH*	*Calcitonin*
Blood calcium	Increased	increased	Decreased
Main action	Absorption from gut	Demineralization	Opposes demineralization
Calcium absorption from gut	Increased	Increased (indirect)	
Bone resorption	Decreased	Increased	Decreased
Effect of excess	Hypercal-cemia +	Hypercal-cemia ++	Hypocalcemia

II- Phosphate metabolism

Eighty-five per cent of body phosphorus is located in the mineral phase of bone. The remainder is present outside bone, largely in an intracellular location as phosphate compounds. In the extracellular fluid, phosphate is mostly inorganic.

Intracellular phosphate has vital functions in:

1- macromolecular structure (e.g. in DNA)

2- energy metabolism (e.g. energy-rich phosphates such as ATP)

3- cell signaling

4- enzyme activation by phosphorylation.

Intracellular phosphate is largely organic as a component of phospholipids, phosphoproteins, nucleic acids and nucleotides (e.g. ATP).

Phosphate Homeostasis

Body phosphate homeostasis is determined by modulation of intestinal uptake of dietary phosphate, renal phosphate reabsorption and excretion, and the exchange of phosphate between extracellular and bone storage pools.

PTH reduces the reabsorption of phosphate from the proximal tubule of the kidney, which means more phosphate is excreted through the urine.

However, PTH enhances the uptake of phosphate from the intestine and bones into the blood. In the bone, slightly more calcium than phosphate is released from the breakdown of bone.

In the intestines, absorption of both calcium and phosphate is mediated by an increase in activated vitamin D. The absorption of phosphate is not as dependent on vitamin D as is that of calcium.

The end result of PTH release is a small net drop in the serum concentration of phosphate.

III- Magnesium metabolism

Magnesium is the second most abundant intracellular cation. It is essential for the activity of many enzymes, including the phosphotransferases. Bone contains about 50% of the body's magnesium; a small proportion of the body's content is in the ECF.

Plasma [magnesium] is normally kept within narrow limits, which implies close homeostatic control. The serum [magnesium] may be normal although a state of intracellular depletion exists.

Significant amounts are contained in gastric and biliary secretions which may explain the possible toxicity with magnesium in case of obstructive liver disease.

Renal conservation of magnesium is at least partly controlled by PTH and aldosterone.

When the dietary intake is restricted, renal conservation mechanisms are normally so efficient that

depletion, if it develops at all, only comes on very slowly.

Extracellular magnesium is important for normal neuromuscular activity, while intracellular magnesium is an important:

1- as a cofactor for various enzymes and nucleic acids.

2- for normal cellular function

3- for replication

4- production of energy

Normal levels of magnesium are not only necessary for PTH release but may also be required to ensure an adequate end-organ response to PTH.

IV-Iron

Iron is an essential element present mainly in the porphyrin complex, haem, and in iron storage proteins, ferritin and haemosiderin. Haem, which is present in haemoglobin, myoglobin and cytochromes, is formed by the insertion of ferrous iron, Fe2+, into protoporphyrin

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

Dietary iron and iron absorption

The normal intake of iron is about 10–20 mg/day. Good sources are liver, fish and meat.

Normally, about 5–10% of dietary iron is absorbed by the duodenum, and the rate of absorption is controlled by physiological and dietary factors which are:

1- *State of iron stores in the body:*

Absorption is increased in iron deficiency and decreased when there is iron overload.

2- *Rate of erythropoiesis:*

When this rate is increased, absorption may be increased even though the iron stores are adequate or overloaded.

3-*Contents of diet:*

Substances that form soluble complexes with iron (e.g. ascorbic acid) facilitate absorption. Substances that form insoluble complexes (e.g. phytate) inhibit absorption.

4- *The chemical state of the iron:*

Iron in the diet does not usually become available for absorption unless released during digestion. This depends, at least partly, on gastric acid production; Fe2+ is more readily absorbed than Fe3+, and the presence of H+ helps to keep iron in the Fe2+ form. Iron in haem (in meat products) can be absorbed while still contained in the haem molecule. The ferric state of iron should be converted to the ferrous state before being absorbed.

Iron transport, storage and utilization

After being taken up by the intestinal mucosa, iron is either:

(1) oxidized to the ferric state Fe^{3+} and incorporated into ferritin and retained by the mucosal cells which are then lost by sloughing of the mucosal cell, or

(2) transported across the mucosal cells directly to the plasma, where it is carried mainly combined with *transferrin.*

The total iron circulating bound to transferrin is taken up by cells and either incorporated into haem or stored as ferritin (or haemosiderin, probably formed by the condensation of several molecules of ferritin).

In summary, Iron is stored as a ferric state in ferritin., while transported in plasma bounded to transferrin as a ferrous state. Within haemoglobin, iron is present in the ferrous state as well.

Functions of iron

1- It serves as a carrier of oxygen to the tissues from the lungs by red blood cell haemoglobin.

2- A transport medium for electrons within cells

3- An integrated part of important enzyme systems in various tissues.

Iron deficiency

Worldwide, this is the most common single nutrient deficiency which occurs secondary to various medical conditions such as poor iron intake, malabsorption, bleeding, or many other conditions.

In patients who develop iron deficiency,

• serum [ferritin] falls, then

• serum [transferrin] and TIBC increase, after which

• serum [iron] falls, and finally

• anemia becomes evident which is a hypochromic microcytic anemia.

Iron overload

This is much less common than iron deficiency. Diagnosis is not usually difficult once the possibility has been considered. High levels of Iron are toxic and can lead to many organ damages especially the liver and the heart.

Increased serum [iron] with normal [transferrin] (or TIBC) often lead to 100% saturation of transferrin (or TIBC). Serum [ferritin] is increased, often to more than 1000 µg/L.

This condition is most commonly occurs due to :

1- Parenteral administration of iron, including repeated blood transfusions.

2- Hereditary haemochromatosis, which is characterized by increased absorption of iron.

Other trace elements will be discussed in brief:

Trace element	Functions	Clinical Consequences of Deficiency
Zinc	Structural/cofactor role for several enzymes (e.g. alkaline phosphatase, carbonic anhydrase, enzymes of nucleic acid synthesis	Dermatitis, immune deficiency, poor wound healing
Selenium	Structural component of several enzymes including anti-oxidant enzymes such	Cardiac and skeletal myopathy. Possible increased risk of atheroma and some cancers
Copper	Required for the action of several enzymes, Circulates on caeruloplasmin which can increase as part of the acute phase response	Microcytic anaemia, neutropenia. Osteoporosis

Other trace elements

Chromium may be involved in glucose homeostasis; a chromium complex is able to improve glucose tolerance in some diabetics. Malnourished infants may develop severe glucose intolerance that improves with chromium supplementation.

In adults, a syndrome presenting with weight loss, peripheral neuropathy and marked insulin-insensitive glucose intolerance has been described that improves with chromium supplementation.

Molybdenum is a component of xanthine oxidase and some other metallo-enzymes. Its deficiency has been reported to cause xanthinuria, with low serum [urate] and low urinary uric acid output.

Cobalt is necessary for vitamin B12 metabolism.

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