UNIT 9 MINERALS (MACRO MINERALS): CALCIUM, PHOSPHORUS, MAGNESIUM, SODIUM, POTASSIUM, CHLORIDE

Structure

9.1 INTRODUCTION

In the previous units we learnt about the structure, properties, deficiencies/toxicity and recommended dietary intakes of several vitamins. In this unit, we shall brief ourselves about several minerals. As we all know, humans require several mineral elements for optimal functioning. These mineral elements are broadly divided into two classes i.e. macro and micro minerals. Macro minerals, also referred to as major *minerals* are distinguished from micro minerals by their occurrence in the body. Thus, macro minerals constitute at least 0.01% of the total body weight or occur in minimum quantity of 5 g in a 60 kg body. They are required in amounts greater than 100 mg per day. On the other hand, requirement of micro minerals varies from a few milligrams to micrograms per day.

This unit will focus on macro minerals while the next unit (Unit 10) will deal with micro minerals. Before studying individual minerals, you will learn about some common features of minerals. Thereafter, we will briefly go through the salient and important aspects of calcium, phosphorus, magnesium, sodium, potassium and chloride.

Objectives

After studying this unit you will be able to:

- discuss the importance of minerals,
- describe the metabolism, functions, food sources of all the essential macro minerals,
- identify the various deficiency and toxicity symptoms of selected macro minerals,
- explain the significance of interactions among the minerals, and
- identify the dietary requirements of various macro minerals for different age groups.

9.2 GENERAL NUTRITIONAL FUNCTIONS OF MINERALS

We hear and talk about minerals almost everyday with regards to maintaining good health. But what are minerals and what functions do they usually perform? Well, a mineral is *a solid homogeneous crystalline chemical element or compound that results from the inorganic processes of nature.* Different minerals perform their own respective specialized functions and have a variety of roles to perform. Before we deal with the function of each of these, let us brief ourselves with their overall functions. The varied functions of minerals can be grouped under four general physiologic roles viz.:

- *Structural:* They form an integral part of structures such as the bones/skeleton, blood etc.
- *Catalytic:* Certain minerals are required as constituents of enzymes, co-enzymes in various metabolic pathways.
- *Cellular:* Some are necessary for membrane stability, as well as, inter and intra cellular transport mechanisms.
- *Others:* They play an important role in muscle contraction, nerve transmission etc.

In the previous section wc read about the difference in the requirements of various macro and micro minerals. Well, the functions of macro and micro minerals may also be different. For instance, macro minerals largely perform structural functions e.g. 99% of body calcium, 85% of phosphorous and 50-60% of magnesium is in the bone and is calcified tissue. Besides this, phosphorus is an important component of phospholipids and phosphoproteins that form important structural component of the cell membranes. Some macro minerals, in addition to their structural role, are involved in catalytic function e.g. magnesium exerts catalytic and regulatory role in number of biochemical reactions. Calcium functions as a messenger in signal transduction in nerve and muscle cells, as you may recall studying earlier in the Applied Physiology Course (MFN-001) in Unit 9. Phosphorus, by way of phosphorylation-dephosphorylation cycle, is involved in the regulation of enzymes.

Micro minerals are found in small quantities (parts per million or parts per billion) in tissues and cells function primarily as a part of enzymes. They are present at the active site or are regulators of enzymatic activity. As component of enzymes, they often participate in *redox reactions* (i.e. oxidation/reduction reactions) and function as the electron carrier. Metalloproteins and metalloenzymes containing iron (Fe), selenium (Se), copper (Cu), manganese (Mn) function in a variety of redox and respiratoiy chain enzymes and proteins. Certain micro minerals provide binding sites for the enzyme-substrate combination e.g. zinc.

A major portion of the iron in the body is present in haeinoglobin, and a smaller proportion as component of several enzymes. Similarly, zinc, besides its catalytic role, exerts a structural role in protein synthesis, particularly as zinc finger protein which is involved in *gene transcription. Gene transcription,* as you may be aware, is *the synthesis of mRNA from the complementary strand of DNA.* We will learn about this aspect in unit 19 later in this course.

Although macro minerals are mainly involved in structural role while micro elements are involved in catalytic role, there seems to be some overlap, for some minerals, Specific functions of each will be dealt with in the following sections.

Next, we shall quickly brief upon the overall absorption and metabolism of minerals.

9.3 ABSORPTION AND METABOLISM OF MINERALS

All minerals in the diet are not equally absorbed. Also different compounds and complexes of same mineral are absorbed with different degree of efficiency. *The fraction of the dietary intake of minerals absorbed and utilized for specific functions is defined as the bioavailability of the minerals.* In addition to the chemical form in which minerals are present in the diet, factors such as age, sex, general health, and other constituents of the diet affect bioavailability of minerals.

Upon absorption across the intestinal mucosa, minerals enter their metabolic pool. They are transported in the blood by specific transport protein(s) to their storage site or to the active physiologic/biochemical site.

The physiologic effects of minerals depend on the level of intake. There is a range of intake, known as *safe and adequate range* which provides optimal function. If the intake is p ogressively below this range there is a gradual decrease in the respective function of minerals until overt signs of deficiency appear. On the other hand when the intake exceeds the *upper limit* of *safety* (i.e. upper tolerable limit) signs of toxicity begin to appear. In fact, all the essential minerals are toxic if consumed in excess; however the concentration at which toxicity occurs varies widely. It must be emphasized here that as long as a mixed diet is the only source of minerals, toxicity is most unlikely to occur.

In our subsequent sections we will learn in detail about the metabolism, functions, requirements, food sources etc of calcium, phosphorus, magnesium, iron, sodium, potassium and chloride. Let us begin with one of the most crucial element for maintaining bones and our skeletal system i.e., calcium and learn why is this mineral so important for us?

9.4 CALCIUM

Among minerals, calcium (Ca) is the most abundantly present in humans, representing 52% of the body's mineral content and amounting to 1.2% of body weight.

In the elementary composition of the human body, calcium ranks fifth after oxygen, carbon, hydrogen and nitrogen, and it makes up 1.9% of the body by weight. Nearly all (99%) of total body calcium is located in the skeleton. The remaining 1% is equally distributed between the teeth and soft tissues, with only 0.1% in the extracellular fluid (ECF).

You all must be aware of the food sources of calcium. However, we will quickly review them.

Food Sources

Dairy products are of course the primary source of calcium followed by grains and pulses. Among the millets, ragi contains substantial amount of calcium. The bio-availability of calcium from different dietary sources is variable. For instance, phytates in whole grain cereals inhibit calcium absorption. Fermentation, on the other hand, reduces phytate content and improves calcium absorption. We will learn more on calcium bioavailability later in this section. The calcium content of some important foods is given in Table 9.1.

Table 9.1: Calcium content of some calcium-rich foods (mg/100 g edible portion)

Food	Calcium Content	Food	Calcium Content
Cereals/Millets		***Green Leafy Vegetables***	
Ragi	344	Agathi	1130
Amaranth seeds	510	Amaranth	397
Pulses		Fenugreek	395
Bengal gram whole	202	Rape leaves	370
Horse gram whole	287	***Milk & Milk products***	
Rajmah	260	Cow's milk	120
Nuts and Oilseeds		Buffalo milk	210
Gingelly seeds	1450	Cheese	790
Mustard seeds	490	Khoa	956
Cumin seeds	1080	***Fish & Sea foods***	
Poppy seeds	1584	Hilsa	180
		Rohu	650

Source: Nutritive Value of Indian Foods by C. Gopalan, B.V. Ramasastri, S.C. Balasubramanium, revised and updated by B.S. Narasinga Rao, Y. G. Deosthala and K.C. Pant, NTN, 1989.

Next, let us learn about the metabolic fate of calcium in our body.

Absorption, Transport *and* Excretion

Calcium (Ca) in food occurs as calcium salts e.g. calcium phosphate or is associated with other dietary constituents e.g. calcium caseinate in milk. Before absorption, Ca must be released from foods and solubilized. This is achieved by the combined actions of gastric acid, intestinal enzymes, intestinal contractions and peristalsis. When calcium intake is low, calcium is mainly absorbed by active (transcellular) transport, but at higher intakes, an increasing proportion of calcium is absorbed by simple (paracellular) diffusion. Thus, calcium is absorbed from the intestine by *transcellular* route and paracellular route. What are these routes? Let us discuss each one of these in detail.

Transcellular Route: It operates primarily in the duodenum and proximal jejunum. It is stimulated when Ca ingestion is lower relative to requirement. It is a metabolically active process, which means energy in the form of ATP is required to absorb and transport the calcium across the intestinal mucosal cells,

Transcellular movement involves 3 sequential steps, The first from the intestinal lumen to the intestinal mucosal cells across the brush border, the second within the cell from the lumen to the serosal side and finally the third, extrusion from the cell into the blood circulation. All three steps are regulated by *calcitriol* (1,25 di- hydroxy cholecalciferol), the biologically active hormone form of vitamin D_3 about which you may recall studying earlier in Unit 7.

Paracellular Route: It involves passive Ca transport through the tight junctions between mucosal cells. The salient features include:

- It is independent of nutritional and physiological regulation.
- It is concentration-dependent and occurs when there is an increased intake or a person is taking supplements.
- It occurs throughout the small intestine, ileum being the important site.

Thus, we can say that most Ca absorption takes place in the small intestine. There is some evidence, which suggests that not more than 4% (8 mg) of dietary Ca is absorbed by the colon per day. The unabsorbed component which appears in the faeces together with the unabsorbed component of digestive juice calcium is known as endogenous faecal calcium. The faeces, therefore, contain unabsorbed dietary

calcium and digestive juice calcium that was not reabsorbed. *True absorbed calcium* is *the total amount of calcium absorbed from the calcium pool in the intestines* and therefore contains both dietary and digestive juice components. *Net absorbed calcium is the difference between dietary calcium and ,faecal calcium* and is numerically the same as true absorbed calcium minus endogenous faecal calcium. At zero calcium intake, all the faecal calcium is endogenous and represents the digestive juice calcium which has not been reabsorbed; net absorbed calcium at this intake is therefore negative to the extent of about 200 mg (5 mmol). When the intake reaches about 200 mg (5 mmol), dietary and faecal calcium becomes equal and net absorbed calcium is zero. As calcium intake increases, net absorbed calcium also increases, steeply at first but then, as the active transport becomes saturated, more slowly until the slope of absorbed or ingested calcium approaches linearity with an ultimate gradient of about 5-10%. True absorption is an inverse function of calcium intake, falling from some 70% at very low intakes to about 35% at high intakes.

There are several factors which influence the amount of calcium absorbed through the intestine. These factors can thus be related to the bioavailability of calcium. The subsequent discussion will look at these factors in detail. But first we shall look at the excretion of unabsorbed calcium.

Excretion: Calcium is excreted approximately in equal amounts in urine and through intestinal secretions. Bile and other secretions into the intestine account for 150 mg calcium per day of which 30% is reabsorbed. The minimum endogenous (from the body as distinguished from exogenous which is from the diet) excretion of calcium is thus 100 mglday (2.5 inillimoles). Urinary calcium excretion varies greatly among individuals and varies from 2.5-6.0 millimoles/day (100-240 mglday). Urinary and endogenous faecal calcium are not the only forms of excreted calcium; losses through skin, hair and nails also need to be taken into account (insensible losses). Sweat losses are minimal, about 15 mglday. Total calcium loss may thus amount to 350 mglday.

Moderate to high intakes of sodium increases renal excretion of calcium. An intake of 500 mg of sodium as sodium chloride was found to draw out 10 mg of calcium in the urine. One study in post menopausal women found a correlation between high urinary sodium excretion and increased bone loss from the hip.

Another factor that increases urinary calcium losses is high intake of protein. In typically vulnerable groups like post menopausal women, in whom decreased oestrogen production is associated with accelerated bone loss, 3% of the skeletal mass per year, it is advisable to regulate sodium intake and avoid high protein intakes. However, the data are very insufficient to make any adjustments in requirements of the general population based on sodium intake. Reduced sodium intake can have other advantages such as control of high blood pressure.

Now that we have studied about the excretion of calcium, let us get back to the factors, which influence calcium absorption.

Factors Affecting Calcium Absorption

It is a well known fact that the amount of calcium that we eat need not be the amount of calcium that gets absorbed. The difference between the two is primarily due to certain factors which may hinder/enhance the absorption or bioavailability of calcium. Thus, the *bioavailability of calcium* can be defined as *the fraction of dietary calcium that is potentially absorbable by the intestine and can be used for physiological functions, particularly bone mineralization or to limit bone loss.*

Several factors affect the proportion of dietary calcium absorbed by humans, also known as *fractional absorption of dietary calcium.* The fractional absorption varies inversely with the quantity of calcium ingested. Lower the intake, higher the percentage of calcium absorbed. A study on healthy adult women, in which intakes were lowered from 2000 mg calcium per day to 300 mg per day (i.e. from 50 to 7.5 millimoles/day), the fractional whole body retention of ingested calcium, an index

of absorption increased from 27% to 37%. It should be noted that this adaptation does not fully make up for the increased losses on higher intake. In absolute amounts, the women would have absorbed much more calcium on 2000 mg intake versus 300 mg. This adaptation was reported to take 2-3 weeks, and was accompanied by increase in 1,25 di OH D_3, which as already seen, increases intestinal absorption of calcium.

Age is another factor which influences the absorption of calcium. Fractional absorption of calcium is highest in infancy i.e., 60%, followed by the early pubertal period. One study found 28% calcium absorption in pre pubertal children that increased to 34% in early puberty returning to the adult value of 25% two years later. Absorption of calcium is also increased in *pregnancy* to levels higher than 25% reported for adults. Available data suggests that in post menopausal women, absorption declines by 0.21% every year. Thus, from 50 years Io 70 years, absorption may decline by 4%. Ageing also reduces renal losses of calcium, due to reduced absorption and decrease in filtered calcium load.

Several dietary constituents have an effect on calcium absorption. The differences in fractional absorption from different foods can be partly explained by their constituents. Calcium is poorly absorbed from foods that are rich in oxalic acid or phytic acid. Phytates, present in the husk of many cereals, as well as, in nuts, seeds, and legumes, can form insoluble calcium phytate salts in the gastrointestinal tract. Excess oxalates can precipitate calcium in the bowel. In comparison to calcium absorption from milk, calcium absorption from phytic acid rich grains is one half and from spinach it is only one tenth. This is so because spinach is high in oxalic acid. Among the dietary factors, which increase calcium absorption, lactose is prominent. In fact all metabolizable sugars have been shown to increase calcium absorption. Table 9.2 summarizes the current factors known to affect calcium absorption.

Table **9.2:** Various factors **influencing calcium** absorption

Factors	Effect **on Absorption**	**Possible** Mechanism (s)
A Physiological Factors		
1) Ca Deficiency	Increases	Stimulates PTH, which in turn increases calcitriol, that in turn increases intestinal absorption.
2) Pregnancy & Lactation	Increases	Increased requirement & stimulates. trans-cellular route.
3) Ageing	Decreases	With age, efficiency of renal calcitriol production in response to PTH reduces, thereby reducing intestinal absorption.
4) Menopause	Decreases	Oestrogen deficiency reduces vitamin D mediated Ca absorption.
5) Malabsorption syndrome	Decreases	In steatorrhoea, unabsorbed Patty acids form insoluble Ca soaps, and inhibit calcium absorption.
B ***Dietary Factors***		
1) Lactose	Increases	Possibly improves Ca solubility in the intestine.
2) Sugar, sugar alcohols, protein, xylitol	Increase	
3) Phytates	Decreases	Binds Ca molar ratios of more than 0.2. Phytate:Ca increase risk of deficiency, by forming insoluble calcium-phytate complexes.
4) Oxalates	Decreases	Chelates and increase faecal excretion
5) Non fermentable Fibers	Decreases	Results in reduction in transit time and less time for absorption.

The presence of substances which form insoluble complexes with calcium, such as the phosphate ion also influences calcium absorption. High calcium-phosphorus ratio increases calcium absorption. The relatively high calcium-phosphate ratio of 2.2 in human milk compared with 0.77 in cow milk may be a factor in the higher absorption of calcium from human milk than cow milk.

Intestinal calcium absorption is mainly controlled by the serum concentration of 1,25-$(OH)_2D$ as discussed above. The activity of the 1-α-hydroxylase, which catalyzes 1,25-$(OH)_2D$ production from 25-hydroxyvitanlin D (25-OH-D) in the kidneys, is negatively related to plasma calcium and phosphate concentrations and positively related to plasma parathyroid hormone concentrations. Thus, the inverse relationship between calcium intake and fractional absorption described above is enhanced by the inverse relationship between dietary calcium and serum 1,25-$(OH)_2D$. We will learn about this aspect later in this section under the heading *regulation of Ca concentration.*

Absorption from dietary calcium supplements is important to know, since they are almost universally recommended for post menopausal women. As far as supplement tablets are concerned, tablet disintegration is an important consideration. In one study, absorption from different supplements were studied under similar test conditions and compared with absorption from milk. When 250 mg of calcium was given along with breakfast meal, the absorption was from calcium-citrate-inalate (35%), calcium carbonate (27%) and tri calcium phosphate (25%) which was similar to the calciuin absorption from milk (29%). Another finding of importance is that calcium from calcium carbonate in achlorhydric patients is reduced only when taken on an empty stomach. When taken with a meal, the absorption is greatest when calciuin is taken in doses of 500 mg or less and with foods.

We have so far learnt about the absorption of calcium and the factors which influence calcium absorption. It would be interesting to note here that majority of the calcium absorbed is stored in the bones/skeletal tissues. You may also have observed altered blood and bone calciuin levels during clinical conditions involving a low intake. We shall now learn about calcium homeostasis and the inter-relationship of blood calcium with bone calcium and other tissues of the body.

Tissue Distribution and Regulation of Calcium Concentration

As already discussed, development and preservation of bone mass is quantitatively an important function of calcium. It should also be noted here that the calcium content of the body at birth is only 30 mg which increases to 1000-1200 g by adulthood through deposition of mineral in the skeleton. It is not surprising, then, that of 1200 g calcium found in an adult human, 99% is present in bones and teeth. The remaining 10% found in blood, extracellular fluid (ECF), muscles and other tissues, nevertheless plays an important role in vascular contraction, vasodilation, muscle contraction, nerve transmission and glandular secretions. The concentration of ionized calcium in blood plasma is very critical for their functions and therefore the plasma calcium is controlled within very narrow limits, the skeletal calciuin providing a large reserve for doing this. Thus, calcium in plasma is present in three major fractions:

- Ionized calcium
- Protein bound calcium
- Complexed calcium

The ionized calcium that constitutes 50% of the total plasma calcium is the only biologically active fraction. Of the remaining half 40% of the plasma calcium is protein bound, 80%being bound to albumin and 20% to globulin. Although the protein bound calcium, does not participate in the biological actions, it serves as a ready

reservoir of ionized calcium. When plasma calcium levels fall, the first line of defense against hypocalcemia is the dissociation of the calcium from the protein complexes to make the cation Ca^{++} available. About 8% of plasma calcium is present as complexes with organic phosphate. This has little importance as a reservoir of ionized calcium.

The regulation of plasma calcium is finely controlled by three sets of hormones and these are crucial for maintaining plasma level constant in the long term. The normal range for total serum calcium is very narrow i.e. 2.0-2.5 millimoles per litre (9-10 mg/dl) when plasma protein concentrate are normal, total plasma calcium less than 2.2 millimoles/litre reflects hypercalcemia. Let us read a little further about the regulation of extra and intracellular levels of calcium. We will first talk about plasma calcium concentration.

a) *Regulation of Plasma Ca^{+2} Concentration:* The concentration of ionized Ca in plasma is maintained within range by regulating processes such as absorption, excretion, secretion and storage in the bone. This tight regulation is achieved through the following three hormones:

- *parathyroid hormone* (PTH),
- *calcitriol* (1,25 $(OH)_2$ D_3), and
- *calcitonin*.

When the plasma Ca concentration is low, parathyroid gland is stimulated to secrete PTH. To some extent, high plasma phosphorus level stimulates secretion of PTH. PTH increases plasma Ca concentration by following interactions:

- In bones, PTH promotes resorption (dissolution of bone calcium) that is added to the blood.
- In kidney tubules, PTH also increases reabsorption of Ca, thus conserving calcium plasma.
- In kidney, PTH also increases the synthesis of calcitriol. Calcitriol acts on the small intestine to promote calcium absorption, thus adding calcium to the blood.

Calcitonin, in contrast to PTH, serves to lower serum Ca^{+2} by preventing dissolution and mobilization of Ca^{+2} from bone.

The serum calcium concentration varies despite large changes in dietary calcium because of endocrine control of this mineral.

Next, we shall discuss about the maintenance of intracellular levels of calcium.

b) *Regulation of intracellular Ca concentration:* The cytoplasmic calcium concentration is regulated by a series of calcium pumps, which either concentrate calcium ions within the intracellular storage sites or extrude them from the cells (where they flow in by diffusion). The physiology of calcium metabolism is primarily directed towards the maintenance of the concentration of ionized calcium in the ECF. This concentration is protected and maintained by a feedback loop through calcium receptors in the parathyroid glands, which control the secretion of parathyroid hormone (see Figure 3.1). This hormone increases the renal tubular reabsorption of calcium, promotes intestinal calcium absorption by stimulating the renal production of 1,25-dihydroxyvitamin D or calcitriol [1,25-$(OH)_2D$], and, if necessary, resorbs bone. However, the integrity of the system depends critically on vitamin D status; if there is a deficiency of vitamin D, lhe loss of its calcaemic action leads to a decrease in the ionized calcium and secondary hyperparathyroidism and hypophosphataemia. This is why experimental vitamin D deficiency results in rickets and osteomalacia whereas calcium deficiency gives rise to osteoporosis.

Thus, intracellular cytoplasmic calcium concentration is maintained by the following mechanisms:

a) Limited entry rate, governed by limited number of calcium channels.

b) Efficient extrusion where by ATP – dependent Ca transport system pumps Ca^{+} out of the cell. In addition, a calcium pump can drive calcium into mitochondria matrix for storage as calcium phosphate until needed.

c) Sequestration of Ca^{+2} in the endoplasmic reticulum or in the case of muscle in the sarcoplasmic reticulum.

It must be evident from the discussion above that calcium levels in bones, blood and other tissues is maintained by a complex interaction of several mechanisms. This itself is suggestive of the fact that calcium forms an integral and important part of these tissues. In our subsequent discussions, we will be able to identify the reasons behind the significance of maintaining adequate levels of calcium in our body. Let us then brief ourselves regarding the functions of calcium.

Functions

Calcium salts provide rigidity to the skeleton and calcium ions play a role in many if not most, metabolic processes. In the vertebrate skeleton, rigidity is provided by a form of calcium phosphate which approximates hydroxyapatite $[Ca_{10}(OH)_2(PO_4)_6]$ and is embedded in collagen fibrils.

Let us get to know the role of calcium in mineralization of bones.

Mineralization of Bones

An understanding of the role of calcium in skeletal structures requires that the process of bone formation and mineralization be clearly comprehendecl. Bone is a unique living tissue as it is rigid and strong and at the same time light enough to be moved by coordinated muscle contractions. There are two types of bones: the *cortical bone,* densely packed mineralized collagen laid down in layers and the *trabecullar bone* (cancellous bones), which is spongy and provides strength and elasticity. Cortical bone is the main component of long bones of the extremities while cancellous bone is a component of the axial (central part of the body such as the spine) skeleton. Defective cortical bones lead to long bone fractures while defective trabecullar bones leads to vertebral fractures.

Two-thirds of the weight of bones is due to minerals and the remaining one-third is due to water and collagens. Bone is continuously resorbed (dissolved) and formed throughout life and there are three major types of bone cells that play an important role in this process. The *osteoblnsts* are actively involved in the synthesis of matrix components of bones (i.e. collagen) and in the transport of calcium and phosphate involved in the mineralization of collagen, crucial to bone formation. Once the protein matrix is laid down, and mineralization begins, the osteoblasts are transformed into *osteocytes,* the second type of bone cells. Protein synthesis reduces at this stage and the osteocytes develop multiple processes that connect the osteocytes with each other. The main function of the osteocytes is to translocate the minerals from surface to in and out of the bone until the bone formation is complete. Osteocyte is multinucleated giant cell that resorbs bone. The *osteoclasts* have all the enzymatic components which when secreted will solubilize the matrix and release the calcium and phosphorous, that are added to the blood, travelling via the ECF.

In children and adolescents, skeletal turnover occurs such that formation of bone exceeds resorption. Ca accumulates in the skeleton at an average rate of 150 mg/day. In adulthood, skeleton turn over continues such that activities of osteoblasts and osteoclasts are in equilibrium. From 50 years in men and from menopause in women, bone balance becomes negative.

As discussed earlier, in addition to the structural role in bones, Ca also performs many other functions in the body. These functions include:

- Clotting of blood
- Nerve conduction
- Muscle contraction
- Enzyme regulation
- Membrane permeability

Ionized Ca is chiefly involved in these functions. As the levels of serum total and ionic calcium are tightly controlled, these functions are well regulated. Bone mineral serves as the ultimate reservoir for the calcium circulating in the ECE Many neuromuscular and other cellular functions depend on the maintenance of the ionized calcium concentration in the ECF. Calcium fluxes are also important mediators of hormonal effects on target organs through several intracellular signalling pathways, such as the phosphoinositide and cyclic adenosine monophosphate systems.

It can be concluded from the discussions above that our body requires considerable quantities of calcium in order to create and maintain its skeletal structures and perform other important functions such as clotting of blood. Adequate intake of calcium is thus important to maintain a good physiological status. In our subsequent discussions, we will learn about the relevance of calcium levels in different tissues and what should be the ideal intake of calcium to maintain calcium homeostasis in the body.

Assessment of Calcium Status and Calcium Requirements

There is no biochemical indicator, which can clearly reflect calcium status. It has also been seen that in case of dietary calcium deficiency; plasma levels are maintained at the cost of bone calcium. Thus, prolonged calcium deficiency will affect the skeletal calcium rese ves. Therefore measures of bone mass may be used as indicators of calcium status. These include: *Bone Mineral Content (BMC)* and *Bone Mineral Density (BMD)*.

BMC is the amount of mineral at a particular skeletal site such as femoral neck, lumbar spine or total body. *BMD* is BMC divided by the area of the scanned region. Besides their relationship to bone mass and strength, BMD and BMC are strong predictors of fracture risk and thus functional indicators of Ca status,

So how much amount of calcium should we consume to ensure that adequate levels are maintained in the bones, blood and other essential tissues? Let us find out.

Dietary Calcium Requirements

There are variations in the amount of calcium recommended by different advisory groups. This is mainly due to the different criteria used as the basis for estimating requirements. The *factorial approach* is the most common one for determining the calcium needs. In this approach, estimates of how much calcium is deposited in the body on a daily basis are made for infants, children and adolescents and for each group and this is added to the endogenous' calcium losses through different routes. The total of this is converted to dietary calcium by using the fractional absorption rates observed at different life stages. A recent refinement involves the use of mathematical modeling of experimental data from balance studies to estimate the optimal calcium intakes at or above which calcium retention is maximal or desirable.

Another approach is to *estimate the optimal calcium intake for bone health,* in terms of reduced risk of osteoporosis in later life. Lack of quantitative data in support of this approach is a constraint in using it widely, Calcium requirements have been

measured by long-term balance studies. With respect to the desirable intake of phosphorus, it is suggested that an elemental Ca:P ratio of 1:1 may be maintained in most age groups except in infancy where the ratio suggested is 1:1.5. We shall learn about phosphorus in the next section.

Requirements for calcium depend upon the rate at which calcium is incorporated into bone; they are therefore highest during periods of growth, especially during infancy and adolescence and fall after peak bone mass is achieved at about 25 years of age. The RDA for Indian adult male is based on replacing the losses of calcium in urine, stools, bile and sweat, which is estimated to be 700 mg calcium per day. The fractional absorption in adults is taken to be 20-30% in the presence of adequate vitamin D. Additional calcium for growth, pregnancy and lactation are calculated separately. The ICMR recommended dietary intake per day for calcium has been given in Table 9.3.

Table 9.3: Daily requirements of **calcium and** phosphorus **for Indians**

Group	**Calcium mg/day**	Phosphorus **mg/day**
Adult man	400	400
Adult woman	400	400
Pregnant woman Lactating woman	1000	1000
Infants (0 - 6m) (6 - 12m)	500	750
Children		
1 - 3 yrs 4 - 6 yrs 7 - 9 yrs	400	400
Adolescents 10 - 12 yrs		
Boys	600	600
Girls	600	600
13 - 15 yrs		
Boys	600	600
Girls	600	600
16 - 18 yrs		
Boys	500	500
Girls	500	500

Source: Recommended Dietary Allowances for Vitamins, Dietary Guidelines for Indians, NIN, ICMR, Hyderabad, India (1998).

How do these requirements compare with other recommendations, particularly the FAO/WHO 2004 recommendations for calcium? Look at Table 9.4, which presents the current recommendations of the FAO/WHO, Canada/United States and the United Kingdom. You may have noticed that our recommendations are different then these, particularly for ethnic or dietary reasons. The FAO/WHO 2004 recommendations for adults are very close to those of Canada and the United States but higher than those of the United Kingdom, which do not take into account insensible losses.

It is important to remember that if the intake of calcium is not adequate, normal levels of calcium cannot be maintained in the blood and other tissues. So, what would happen when the calcium equilibrium gets disturbed? What clinical signs may develop due to a deficient or low intake? The subsequent discussion deals with these issues.

Deficiency and Toxicity

Dietary calcium intake above or below the requirements can result in the elicitation of several signs of deficiencies and excess. Let us first talk about the deficiency of calcium.

Deficiency

If there is a continued inadequate intake or poor intestinal absorption of calcium, plasma calcium concentrations will be maintained from increased bone resorption. The cumulative effect of calcium depletion on the skeleton over many years contributes to the increasing frequency of fractures with age. Prolonged inadequate calcium intake in young growing children will reduce the rate of accretion of the skeleton and may prevent the attainment of the genetically determined maximal bone mass. In extreme cases, Ca deficiency can give rise to rickets in children. Let us discuss the effects of calcium deficiency one by one.

Table **9.4:** Current calcium intake recommendations(mg/day)

Group		FAO/WHO 2004[b]	Canada and United States 1997[a]	United Kingdom 1991"
Infants	0-6 months			
	Human Milk	300		
	Cow Milk	400	210 - 270	525
	7 - 12 months	400		
Children	1 - 3 years	500		
	4 - 6 years	600	500 - 800	350-550
	7 - 9 years	700		
Adolescent				
	Boys 10 - 18 years	1300*	1300	1000
	Girls 10 - 18 years		1300	800
Adults	Females			
	19 years to menopause	1000	1000	*700*
	Post menopause	1300	1200	*700*
	Males			
	19 - 65 years	1000	1000	*700*
	65+ years	1300	1200	*700*
Pregnant Women				
	(last trimester)	120	1000- 1300	*700*
Lactating Women		1000	1000 - 1300	1250

[a] Adequate intake; [b] Reference nutrient intake; * particularly during the growth spurt

Source: Vitamin and Mineral Requirements in Human Nutrition. World Health Organization and Food and Agriculture Organization of the United Nations 2004; Food and Nutrition Board. *Dietary reference intakes for- calcium, phosphorus, magnesium, vitamin D and fluoride.* Washington, *DC,* National Academy Press, 1997; Department of Health. *Dietary reference values jor food energy and nutrients for the United Kingdom,* 1991.

Calcium and Osteoporosis: Gain in bone mass occurs throughout childhood; however, during adolescent growth spurt, the gain in bone mass, as well as, calcium retention is accelerated two to three times more than at younger ages in both boys and girls, The bone mineral content continues to increase beyond the growth spurt into the middle of the third decade. Progressive increase in total body calcium have been shown in one study upto 30 years in female subjects of 19-30 years on an average calcium intake of 700 mg per day. Thus, peak bone mass may be achieved 5-10 years after longitudinal bone growth has been completed. Achievement of adult height is an indication of completion of longitudinal growth.

There is some data to show that increased calcium intakes in children beyond their habitual intakes could increase bone mineral density. What needs to be established is whether such increase in bone density could contribute to increased peak bone mass (i.e. maximum bone mass attained by the middle third decade). The other factor of importance contributing to increased bone mineral density and peak bone mass is weight bearing exercise. The current recommendations in fact focus on adequate dietary calcium intakes and exercise to promote acquisition of peak bone mass and density fracture risks due to osteoporosis at later ages can be reduced.

Accelerated bone loss with age is a consistent finding in both women and men. It occurs earlier in women than in men as decreased oestrogen production in menopause is associated with accelerated bone loss in women, estimated at 3% per year in the first five years after menopause. The effectiveness of calcium supplements in retarding bone loss in post menopausal women is not entirely settled. However, clinical trials in this area seem to indicate that supplements of calcium can have beneficial effect in slowing the rate of bone loss in post menopausal women. The amounts recommended by different advisory groups differ considerably. It seems prudent to recommend that women with calcium intakes below 400 mg per day may benefit by increasing their dietary intakes or by taking supplements of calcium. This is supported by a study on two groups of post menopausal women, one with usual intakes less than 400 mg per day and the other with usual intakes between 400-650 mg per day. Calcium supplementation benefited the group with intakes less than 400 mg per day by slowing the rate of bone loss at several sites while supplements were not effective for the group with intakes between 400-650 mg per day. The role of appropriate exercise, in addition to adequate calcium intake, must receive proper attention. The other nutrient in relation to calcium absorption and bone mineral density is *vitamin D*, about which we have already discussed earlier in Unit 7. It must however, be emphasized here that vitamin D nutrition is as important as that of calcium in relation to prevention of osteoporosis and fractures.

An important aspect that we shall discuss now is the relationship of calcium with blood pressure and what is the significance of calcium deficiency with respect to hypertension.

Calcium and Hypertension: Chronic inadequate intake of calcium may play some role in etiologies of hypertension. Calcium deficiency has been linked to hypertension. Numbers of epidemiological studies, animal experiments and human clinical studies have reported an inverse relationship between Ca intake and blood pressure. Meta-analysis of studies reveal that Ca supplementation (median intake 1g of Ca) resulted in reduction in systolic blood pressure in selected hypertensive patients. People who appear to benefit from calcium therapy are those who have low calcium intakes, low ionized calcium concentration or elevated PTH and those who have low renin activity and are salt-sensitive.

The precise nature of the anti-hypertensive action of dietary calcium is not clear. Calcium has a membrane stabilizing vasorelaxing effect on smooth muscle cells. Calcium can exert its effect through other mechanisms also. Salt sensitive, low renin individuals exhibit low plasma ionized calcium concentration, increased urinary calcium excretion and elevated PTH and calcitriol. Further work is still warranted in this aspect.

It is, therefore, clear from our discussion above, that a positive calcium balance (i.e. net calcium retention) is required throughout life. A positive calcium balance is required throughout growth, particularly during the first 2 years of life and during puberty and adolescence. These age groups therefore constitute populations at-risk for calcium deficiency, as do pregnant women (especially in the last trimester), lactating women, post menopausal women and possibly, elderly men.

.We had mentioned about calcium toxicity a little while ago. Hypercalcemia, though rare, can result in the development of serious metabolic complications. A few of these are being discussed below.

Calcium Toxicity

Elevated blood calcium can occur in association with high parathyroid hormone, hyper- or hypothyroid conditions, bone metastasis, vitamin D toxicity, excess intake or absorption of calcium, Addison's disease and with thiazide diuretics. High blood calcium may be asymptomatic or can cause constipation, nausea and vomiting, increased urination, thirst, muscle weakness, kidney failure, irritability, confusion, psychosis and coma. The role of calcium supplements in eliciting hypercalcemia has always been under scrutiny. Since the efficiency of absorption from large doses is poor, no adverse effects have been found with calcium supplements providing up to 2400 mg/day. However, at such high levels, iron absorption is reduced and risk of iron deficiency increases. A practical suggestion would be not to consume high dose of calcium with meals that provide most of the iron. Supplements of calcium do not carry the risk for renal stones in normal individuals but can increase the risk in patients with renal hypercaliuria. In fact, it has been suggested that dietary calcium may protect against renal calculi because it binds dietary oxalate and reduces oxalate excretion.

In 1997, the Tolerable Upper Intake Level (UL) for Ca for adults was set at 2.5 g daily as a part of Dietary Reference Intakes. Toxic effects of a high calcium intake have only been described when the calcium is given as the carbonate form in very high doses; this toxicity is caused as much by the alkali as by the calcium and is due to precipitation of calcium salts in renal tissue (milk-alkali syndrome). However, in practice, an upper limit on calcium intake of 3 g (75 rnmol) is recommended by the FAO/WHO 2004.

So far we have read about the properties, food sources, metabolism, requirements and the effects of deficient/excess intake for calcium in this section. We also read that the requirements and absorption of calcium and phosphorus are interlinked with each other. We shall now proceed our discussions with phosphorus, which we know is closely related to calcium.

9.5 PHOSPHORUS

Phosphorus is the second most abundant element in the human body, comprising 30% of the total mineral content. An adult human body contains approximately 600 g of phosphorus. Most phosphorus like Ca is stored in the bone and teeth in an inorganic metal state, the *hydroxyapatite*. The remaining 15% is distributed in soft tissues in both organic and inorganic form.

Before we proceed with the metabolism of phosphorus, let us quickly brief ourselves on the dietary sources.

Food Source

Phosphorus is widely distributed in food. Food phosphorus is a mixture of both organic and inorganic forms although the relative amounts vary with the type of food. Both animal and plant foods are important sources and include meat, fish poultry, egg, milk and its products, nuts, legumes and cereals. 80% of phosphorus in grains is bound with phytic acid. In milk, 33% is in the inorganic form.

Let us now proceed to the absorption, transport and excretion of phosphorus.

Absorption, Transport and Excretion

As you have seen that food contains both organic and inorganic phosphorus, but most of it is absorbed in its inorganic form. Therefore, organically bound phosphorous is hydrolyzed in the lumen by intestinal *phosphatases.* However, organic phosphate of phytic acid may not be available.

Phosphorus absorption occurs throughout the small intestine, although duodenum and jejunum are important sites. Phosphorus absorption is efficient–60-70%. Ingestion of antacids containing magnesium or aluminium hydroxide can interfere with phosphorus absorption.

It is important to note that unlike calcium, absorption efficiency of phosphorus does not increase on low intake nor any adaptive mechanism is available for the same. Most phosphorus is absorbed by passive concentration dependent process. However, a portion of phosphorus is absorbed by active transport, facilitated by calcitriol. Unabsorbed phosphorus is excreted in faeces. In plasma, phosphorus is distributed in different forms, as illustrated in Figure 9.1,

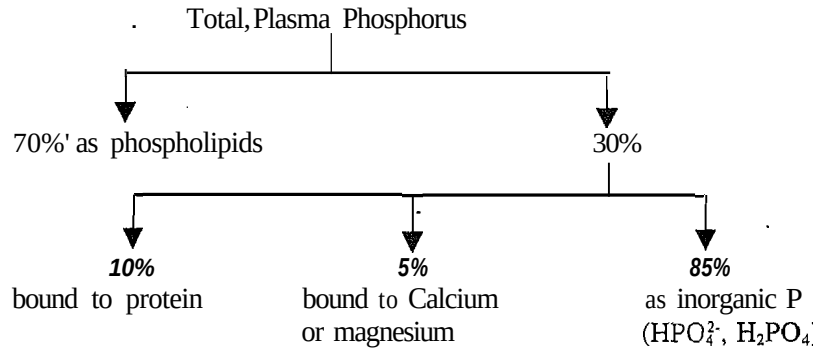

Figure **9.1:** Phosphorous distribution in plasma

Inorganic phosphorus is also referred to as ultra-filterable phosphate and ranges between 2.5 and 4.4 mg/dl in adults. Excretion of endogenous phosphorus is mainly through kidney.

So far we have read about the properties, food sources, absorption, transport and excretion of phosphorus. It would be important to note here that phosphorus shares similar homeostatic mechanisms with calcium and that the phosphate balance is largely maintained by the renal tubules. Keeping this in mind, read the subsequent discussions pertaining to the functions of phosphorus.

Functions

Distribution of phosphorus in body clearly explains that it functions as a structural component, as well as, has a role in metabolic reactions. Also both organic and inorganic forms are important. Important functions of both these forms are explained below:

Inorganic Phosphorus: The major functions of inorganic phosphorus include:

a) *Structural component of bones and teeth:* Phosphorus is a part of calcium phosphate in various crystalline. Ca forms required for ossification. (See section on functions of Calcium)

b) *Acid-base balance*: Within cells, phosphate is the main intracellular buffer.

$$H_2PO_4 \rightleftharpoons H^+ + HPO_4^{2-}$$

Organic Phosphorus: It is involved in the following reactions/components:

a) *Structural component of nucleic acids:* It is important component of DNA and RNA.

b) *Components of cell membrane*: Phospholipids with their polar and non polar regions are important for the bilayer structure of cell membranes.

c) *Component of coenzymes* like NADP, TPP, PLP, coenzyme A, FAD, NAD.

d) Phosphorus is of vital importance in intermediary metabolism of the energy nutrients contributing to temporary storage and transfer of energy in the form of ATP.

e) Many enzymatic activities are controlled by alternating phosphoiylation or dephosphorylation (You may need to recapitulate on this aspect by referring to the regulation of carbohydrate metabolism in the Nutritional Biochemistry Course (MFN-002) in Unit 6). Thus, it is required in regulating metabolism.

For all these functions, it is important to maintain normal level of inorganic phosphate in plasma. However, plasma levels of phosphate are not so closely controlled as those of calcium.

It would be important to note here that like calcium, phosphate metabolism is also regulated by three hormones. These include:

- Parathyroid hormone (PTH),
- 1,25-dihydroxyvitamin D (I, 25–$(OH)_2$ D_3), and
- Calcitonin.

The PTH exerts its regulation primarily by way of the kidney, exerting a phosphaturic effect. When resorption of bones occurs under the influence of increased PTH, the calcium is added to the blood while the phosphates are excreted in the urine.

Vitamin D stimulates intestinal absorption and enhances bone resorption. Its effect on renal handling of phosphate is thought to be indirect. The increase in calcium mediated by 1,25-$(OH)_2$ D_3 suppresses PTH secretion and enhances phosphate reabsorption in the tubules, as you may recall studying earlier under the calcium section.

Finally, let us get to know about the phosphorus requirements.

Dietary Requirements

We read in the previous section that the requirements of phosphorus are closely linked with those of calcium. The phosphorus requirements for different age groups have been mentioned in Table **9.3** earlier. Phosphate requirements are fully met usually when diets provide adequate calcium as these two minerals generally occur together in foods.

However, situations may develop when the phosphate levels in blood and other tissues may increase or decrease beyond normal levels. Such disturbances in the phosphorus levels may develop with or without any effects in the calcium metabolism. We shall now brief upon the clinical conditions of hypo and hyper phosphaternia.

Deficiency and Toxicity

We shall first discuss about low phosphorus levels in the blood.

Inadequate phosphorus intake results in abnormally low serum phosphate levels (hypophosphatemia). The effects of hypophosphatemia may include loss of appetite, anaemia, muscle weakness, bone pain, rickets (in children), osteomalacia (in adults), increased susceptibility to infection, numbness and tingling of the extremities, and difficulty in walking. Seyere hypophosphatemia may result in death. Because phosphorus is so widespread in food, dietary phosphorus deficiency is usually seen only in cases of near total starvation. Other individuals at-risk of hypophosphatemia include alcoholics, diabetics recovering from an episode of diabetic ketoacidosis, and

starving or anorexic patients on refeeding regimens that are high in calories but too low in phosphorus.

High levels of phosphorus are rarely observed, but when they develop it results in the development of several complications. Let us review these in brief.

The most serious adverse effect of abnormally elevated blood levels of phosphate (hyperphosphatemia) is the calcification of non-skeletal tissues, most commonly the kidneys. Such calcium phosphate deposition can lead to organ damage, especially kidney damage. Because the kidneys are very efficient at eliminating excess phosphate from the circulation, hyperphosphaternia from dietary causes is a problem mainly in people with kidney failure (end-stage renal disease) or hypoparathyroidism. When kidney function is only 20% of normal, even typical levels of dietary phosphorus may lead to hyperphosphaternia. Pronounced hyperphosphatemia has also occurred due to increased intestinal absorption of phosphate salts taken by mouth, as well as, due to colonic absorption of the phosphate salts in enemas.

In the section(s) above, we learnt about the properties, food sources, functions, absorption, transport, excretion, as well as, the deficiency and excess of calcium and phosphorus – the most significant macro minerals required by our body. In the next section we shall learn about magnesium, sodium, potassium and chloride. However, before we proceed further, answer the questions mentioned in check your progress exercise 1 to make a quick recapitulation.

Check Your Progress Exercise 1

1) Mention important differences between macro and micro minerals.

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2) Name the following:

a) Hormones regulating plasma Ca^{+2} concentration .....

b) Food sources of phosphorus .....

c) Conditions associated with phosphorus toxicity .....

.....

3) Explain the following

a) Elderly people are more vulnerable to fractures.

.....

.....

b) Plasma Ca levels cannot be used to assess calcium status.

.....

.....

We will now proceed over to yet another important mineral required by our body i.e. magnesium.

9.6 MAGNESIUM

Magnesium (Mg) ranks fourth in overall abundance in body among the cations. It is also the least abundant among macro minerals, the total amount in the body being 25 g. Like Ca and P, this mineral is also present in the bones but unlike them which constitute 99% and 85% of the bones, respectively only 55-60% of total magnesium is located in the skeleton. Another 20-25% is found in muscles with remaining in other soft tissues. Only 1% of total body magnesium is extracellular. Magnesium is closely associated with cells and is the 2nd most abundant mineral in cells after potassium. Let us brief ourselves regarding the food sources of magnesium.

Food Sources

Magnesium is widely distributed in variety of foods and beverages. In plants it is associated with chlorophyll. Thus, green leafy vegetables are excellent sources of magnesium. Most green vegetables, legume seeds, beans, tea, coffee, cocoa and nuts are rich in magnesium, as are some shellfish, spices, and soya flour, all of which usually contain more than 500 mg/kg fresh weight. Although most unrefined cereal grains are reasonable sources, many highly-refined flours, tubers, fruits and most oils and fats contribute little dietary magnesium (<100 mg/kg fresh weight). Corn flour, cassava and sago flour, and polished rice flour have extremely low magnesium contents. Refining of whole cereals can reduce the magnesium content considerably (upto 80%).

We shall now learn about the absorption; transport and excretion of this nutrient.

Absorption, Transport and Excretion

Magnesium absorption to some extent is similar to that of Ca. Absorption of Mg occurs throughout the small intestine, although jejunum and ileum are important sites. It crosses the intestinal membrane by both active transport and passive diffusion. Colon may also play a role in its absorption. About 30-65% of dietary Mg is absorbed in healthy adults. Like Ca, absorption of Mg is also more efficient when its status is marginal or intake is low. Regulation of intestinal absorption is generally thought to occur only for active component of absorption, although mechanism is unclear. Because of chemical similarity of Mg to Ca, it is postulated that vitamin D could regulate its absorption. However, it appears that only large changes in vitamin D intakes could lead to alternations in Mg absorption.

As observed for calcium, some dietary factors influence absorption of Mg, although data supporting this is limited. High intakes of dietary fibre (40-50 g/day) lower magnesium absorption. This is probably attributable to the magnesium-binding action of phytate phosphorus associated with the fibre. However, consumption of phytate- and cellulose-rich products increases magnesium intake (as they usually contain high concentrations of magnesium) which often compensates for the decrease in absorption. The effects of dietary components such as phytate on magnesium absorption are probably critically important only when magnesium intake is low. There is no consistent evidence that modest increases in the intake of calcium, iron, or manganese affect magnesium balance. In contrast, high intakes of zinc (142 mg/day) decrease magnesium absorption and contribute to a shift towards negative balance in adult males. Unabsorbed fatty acids present in 'high quantities (Steatorrhoea) may bind to Mg to form soaps, Lactose, fructose and protein appear to increase its absorption.

In the plasma, most magnesium is found free (55%), some is bound to protein (32%) while small amounts (13%) is cornplexed with citrate, phosphate or other ions.

Magnesium homeostasis is maintained chiefly by controlling its excretion through urine. The kidney has a very significant role in magnesium homeostasis. Active reabsorption of magnesium takes place in the loop of Henle in the proximal convoluted tubule and is influenced by both the urinary concentration of sodium and probably by acid–base balance.

Contrary to calcium homeostasis which is under tight hormonal control, regulation of Mg homeostasis occurs chiefly through renal excretion. About 70% of serum Mg is filtered by kidney, but 95% of this is reabsorbed by a healthy kidney. When the dietary Mg intake is low, renal output of Mg is further reduced. When Mg intake is severely restricted in humans with normal renal functions, Mg output reaches lowest levels of 6 mg/ day (<0.25 millimoles/day) within 5-7 days. Intake of diuretics increases Mg excretion. Similarly thyroid and aldosterone stimulate excretion while PTH inhibits excretion.

Magnesium plays some very important functions in our body. Let us understand the salient ones.

Functions

Like Ca, Mg too has a role in bone formation. Soft tissue magnesium functions as a cofactor of many enzymes involved in energy metabolism, protein synthesis, RNA and DNA synthesis, and maintenance of the electrical potential of nervous tissues and cell membranes. Of particular importance with respect to the pathological effects of magnesium depletion, is the role of this element in regulating potassium fluxes and its involvement in the metabolism of calcium. Some of the important functions of Mg are listed below:

1) Between 50% and 60% of body magnesium is located within bone, where it is thought to form a surface constituent of the *hydroxyapatite* (calcium phosphate) mineral component. Initially, much of this magnesium is readily exchangeable with serum and therefore represents a moderately accessible magnesium store which can be drawn on in times of deficiency.

2) Within cells, Mg is bound to phospholipids of the cell membrane (plasma, mitochondria, endoplasmic reticulum). It helps in membrane stabilization.

3) Mg is responsible for the structural integrity of the subunits forming ribosomes. It also maintains double helical structure of DNA.

4) Intracellular free Mg^{+2} regulates ion movements. It modulates ion transport systems such as Ca pumps and Na-K-ATPase. These are most sensitive to depletion of body Mg^{+2} levels. The impaired activity of these ion pumps is likely to be responsible for the neuromuscular problems that are present during Mg deficiency. The defects would involve difficulty in maintaining the normal movements of Ca, sodium, potassium ions required for nerve conductions.

5) Mg is vital for energy production as it is required by ATP synthesizing protein in the mitochondria.

6) As intracellular component, it is essential for different enzyme reactions, as structural cofactor or an allosteric activator of enzyme activity.

All ATP requiring kinases use ATP in the form of Mg-ATP complex. ATP chelates the Mg ion. Thus, phosphate donating substrate is not ATP but Mg-ATP complex e.g. enzymes in glycolysis.

Some enzymes require Mg-ATP as well as free Mg^{+2}. e.g. carbomyl phosphate synthase of urea cycle.

Mg^{+2} is required by various enzymes participating in the synthesis of carbohydrates, lipids. Mg ions are also required by enzymes that are used in transmitting signals within cells. These enzymes include adenylate cyclase which catalyzes phosphorylation of number of proteins / enzymes, thus regulating metabolic pathways. Because of its function in the formation of cAMP, Mg is involved in mediating the effects of numerous hormones.

Having looked at the functions of magnesium, next let us review the dietary requirements and the asqessment of magnesium status in the body.

Assessment of Magnesium Status and Dietary Requirements

In order to estimate Mg requirements and establish relationship between magnesium intake and deficiency, it is important to have reliable marker/s for diagnosing Mg depletion and its severity. Several indicators of Mg status have been described. These include

i) *Total Serum Mg*: Serum Mg concentration are routinely measured to assess its status. However, extracellular Mg represents only 1% of. the total Mg and appears to be homeostatically regulated. Normal serum levels may occur despite intracellular deficit, But when serum Mg is below normal, the intracellular Mg is definitely lower. Thus, low serum levels can help to detect advanced Mg deficiency.

It is suggested that level of ionized Mg may be more reliable and relevant determinant of deficiency than the total serum Mg, as protein bound Mg is subjected to more variations.

ii) *Magnesium levels in erythrocytes and lymphocytes*: These measures appear to provide a more accurate assessment of body Mg status than serum Mg levels. Peripheral lymphocyte Mg concentration correlate with skeletal and cardiac muscle Mg concentration. Erythrocyte Mg concentration may reflect long term Mg status due to longer span of RBC.

iii) *Level of Magnesium in urine:* Urinary Mg excretion decreases with Mg deficiency. Therefore, Mg excretion before and after administration of an intravenous Mg load could be used to assess status.

As is evident from the above discussion, most methods are expensive, time consuming and not applicable to large populations.

Next, let us learn about the magnesium requirements. Since plant foods are particularly high in magnesium, on a vegetarian diet with plenty of green vegetables, it is unlikely that Mg deficiency will occur. No specific recommendations are made by ICMR for Mg intakes in Indians. However, the FAO/WHO 2004 recommended nutrient intake for magnesium is given in Table 9.5. FAO/WHO recommend 220 and 260 mg magnesium per day for adult females and males, respectively.

Table 9.5: Recommended nutrient intake (RNIs) for magnesium, by group

Group[a]		Assumed Body Weight (kg)	RNI (mg/day)
Infants	0 -6 months		
	Human Milk-fed	6	26
	Formula-fed	6	36
	7 - 12 months	9	54
Children	*1* - 3 years	12	60
	4 - 6 years	19	76
	7 - 9 years	25	100
Adolescent			
	Females 10 - 18 years	49	220
	Males 10 - 18 years	51	230
Adults	Females		
	19 - 65 years	55	220
	65+ years	54	190
	Males		
	19 - 65 years	65	260
	65+ years	64	224

[a] No increment for pregnancy: 50 mg/day increment for lactation.

Source: Vitamin and Mineral Requirements in Human Nutrition. World Health Organization and Food and Agriculture Organization of the United Nations (2004).

Although rare, magnesium homeostasis may get disturbed due to alterations in the metabolism of other nutrients or due to an underlying disease condition. Let us find out more about magnesium deficiency and toxicity.

Magnesium Deficiency and Toxicity

Deficiency of magnesium is rare for two reasons: firstly, the mineral is widely distributed in the foods, secondly, kidney is able to adjust re-absorption of filtered magnesium to body needs. However, Mg depletion occurs in various conditions, which either impair its intestinal absorption or increase its urinary excretion.

Studies have shown that a decline in urinary magnesium excretion during protein–energy malnutrition (PEM) is accompanied by a reduced intestinal absorption of magnesium. The catch-up growth associated with recovery from PEM is achieved only if magnesium supply is increased substantially. Most of the early pathological consequences of depletion are neurologic or neuromuscular defects, some of which probably reflect the influence of magnesium on potassium flux within tissues. Thus, a decline in magnesium status produces *anorexia, nausea, muscular weakness, lethargy, staggering and if deficiency is prolonged, weight loss.* Progressively increasing with the severity and duration of depletion are manifestations of *hyperirritability, hyperexcitability, muscular spasms, and tetany, leading ultimately to convulsions.* An increased susceptibility to audiogenic shock is common in experimental animals. Cardiac arrhythmia and pulmonary oedema frequently have fatal consequences. It has been suggested that a suboptimal magnesium status may be a factor in the etiology of coronary heart disease and hypertension but additional evidence is needed.

Hypomagnesernia associated with deficiency represents a plasma Mg levels of less than 1.5 mg/dl. It leads to impairment in Ca and K homeostatsis. Hypocalcernia and hypokalemia have been observed in both experimentally produced and disease-related Mg deficiency. These disturbances are partially caused by hypomagnesemia induced changes in the production and function of PTH. Reduced serum Mg initially stimulates parathyroid gland to produce more PTH, but as deficiency becomes more severe, the sensitivity of parathyroid gland to a low serum Ca concentration is impaired and level of PTH is low in relation to degree of hypocalcernia.

Decreased Mg status has been suggested as a factor contributing to the pathogenesis of several chronic diseases. Both dysrhythmias and myocardial ischemia have been attributed to low Mg intakes. Hypomagnesemia in diabetes may be one of the risk factors in the development of diabetic retinopathy.

Studies of Mg use in patients with acute myocardial infarction suggest a reduced mortality with rapid post myocardial infarct Mg treatment. Oral supplements in middle aged and elderly women with mild to moderate hypertension has been found to reduce systolic and diastolic blood pressure. However, further research is warranted with respect to the use of Mg supplements.

Let us now brief upon toxicity of magnesium.

It is clear from the dbove discussion that exdessive intake of Mg is not likely to cause toxicity except in people with impaired renal function. Excessive intakes of Mg salts such as $MgSO_4$ can lead to diarrhoea.

In this unit we have read about some important minerals required by our body. In continuation with the same we shall discuss in detail the various aspects of a few other minerals i.e., sodium, potassium and chloride which are often also referred to as *electrolytes*. The significance of these electrolytes lies in their contribution towards maintaining the fluid shift mechanism inter and extracellular. Let us read about these minerals in detail.

9.7 SODIUM, POTASSIUM AND CHLORIDE

Claude Bernard was the first to draw attention to the internal environment (milieu interior), referring to the extracellular fluid (ECF) – a medium in which all cells are bathed. *Homer Smith* presented a convincing argument that "the extracellular compartment contains constituents and concentrations similar to the precambrian seas, which presumably bathed the earliest piimordial unicellular organisms".

As we know that the total body water (TBW) in a 70 kg man is 60% of the body's weight i.e. about 40 litres. Two-thirds of this resides inside the cells, i.e. *the intracellular fluid* (ICF), while one-third is in the *extracellular compartment* (ECF) that bathes the cells. A minor portion about 1 litre is present in the intestines and anterior chambers of the eyes. The most important electrolytes in the ECF are sodium (135-145 millimoles/L and chloride (98-108 millimoles/ L). The concentration of potassium in the ECF is very low, 3.5-4.5 milli moles/L, however, potassium is the predominant cation (K^+) in the ICF, whereas sodium and chloride in the ICF are negligible. Muscle cells have much higher water content than the others and therefore ICF and TBW are closely related to lean body mass.

The three macro minerals, Na, K and Cl are related to each other and hence will be discussed together, which makes it easier to appreciate their roles in metabolism.

You know that Na and K are monovalent cations (ions that carry a positive charge) while Cl is a monovalent anion (ions that carry a net negative charge). All three are known as *electrolytes* as their ions are used for generating electric charge differences across the plasma membrane of most cells.

Na constitutes 2%; K 5% and Cl 3% of the total mineral content of the body. These minerals exist as ions in the body fluids and are principal electrolytes in the body. K is a major intracellular electrolyte while Na and Cl are present in the extracellular fluids. Let us learn about their principal food sources.

Food Sources

The major source of sodium and chloride is common salt added to our food in the form of sodium chloride. Naturally occurring sources of sodium are milk, meats, eggs and most vegetables. In addition, food additives used in processed foods such as baking powder, preservatives etc. contribute towards dietary sodium intake. Therefore, it is important to take note of all these while calculating the sodium content of diets, On the other hand, potassium is abundant in unprocessed foods, fruits, many vegetables and fresh meats. Also many salt substitutes contain potassium instead of sodium.

Absorption of these electrolytes is governed by several factors including body fluids, hormones and presence of other nutrients, to name a few. We shall now highlight the salient features of absorption, transport and excretion of these electrolytes.

Absorption, Transport and Excretion

All these three elements are readily absorbed from the small intestine with almost 90-100% efficiency. They are excreted primarily via urine, although faeces and sweat are other routes of elimination. It is important to note that profuse sweating can result in substantial losses of these elements. Both sodium and chloride are absorbed by the following mechanisms:

a) Sodium glucose and sodium amino acid co-transporters exist in the apical membranes of enterocytes and mediate sodium uptake coupled with glucose or amino acid uptake. Look at Figure 9.2, which illustrates this mechanism.

As seen in Figure 9.2, sodium and glucose/amino acid both bind to the carrier which shuttles them from the outer surface to the inner surface. Here, both sodium and glucoselamino acid are released from the carrier and carrier returns back to the outer membrane. The absorbed Na^c is then pumped out across basolateral membrane by Na^+/K^+-ATPase pump while glucose diffuses across by facilitated transport. Thus, glucose and Na^c are co-transported. Recollect that the oral formula used to correct diarrhoea1 fluid losses always contain glucose and sodium chloride in a single combination. This is the reason why.

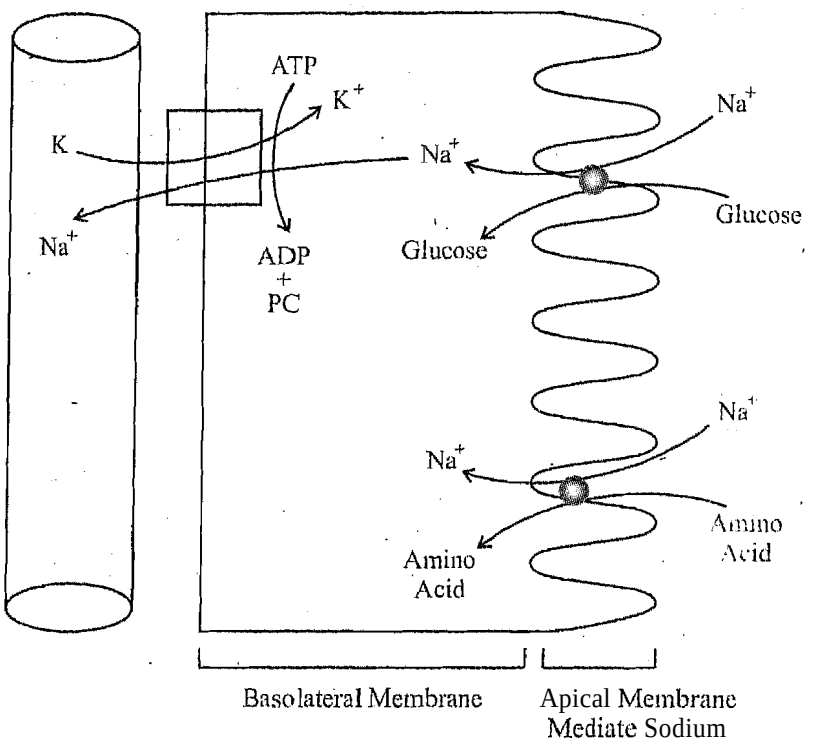

Figure 9.2: Intestinal absorptioh of sodium

b) Another mechanism proposed is electroneutral Na^+ and Cl^- co-transport. This is based on the observation that significant proportion of sodium uptake requires presence of chloride and vice-versa. Na^+ and Cl^- enter the enterocytes and are exchanged for H^+ and HCO_3^-, respectively. Figure 9.3 illustrates the sequence of events.

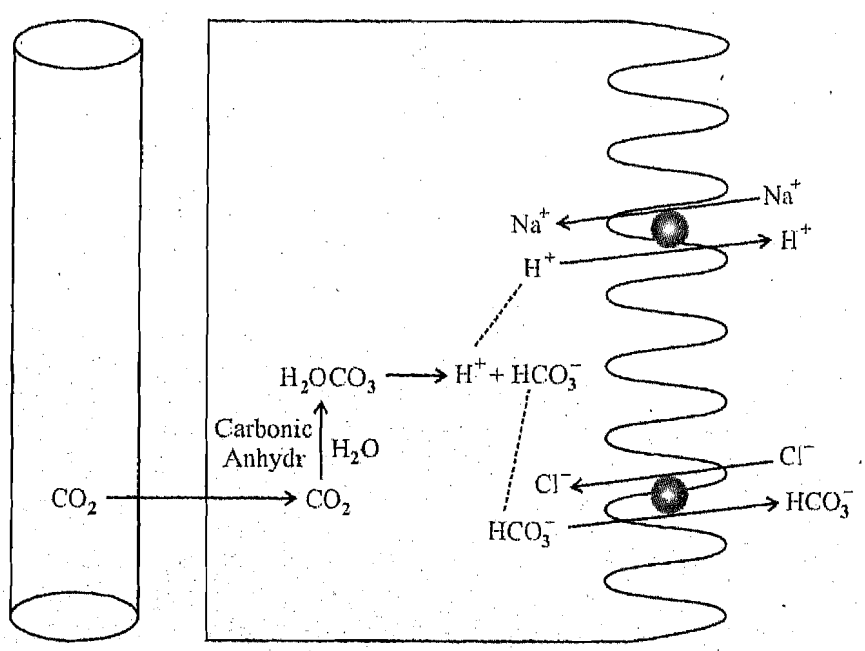

Figure 9.3: Absorption of sodium and chloride

So far we have read about the absorption of sodium and chloride. What about potassium? How is it absorbed? Let us read further to brief ourselves on the mechanism linked to its absorption.

Potassium is absorbed in the small intestine as a consequence of bulk fluid absorption. Both sodium and potassiuin are also absorbed in the distal colon. Sodium enters the luminal membrane of colonic mucosal cells through Na^+ channels and pumped out across the basolateral membrane by Na^+ / K^+-ATPase pump. On the other 'hand, absorption of potassium in the colonic cells is mediated by K^+/H^+-ATPase pump. This exchanges intracellular H^+ for K^+. Potassium then diffuses across the basolateral membrane via the K^+ channel.

We will now discuss about the regulation of normal levels of sodium and potassiuin in the body and a few details about their excretion.

Regulation and Excretion

Renal excretion and retention of these elements is closely regulated. The total content of body sodium especially the concentralion in the extracellular fluid (ECF) is under homeostatic control. Let us see how body regulates Na content in ECF.

Of the total Na filtered through the glomeruli, over 99% is reabsorbed by the kidney tubules. A large proportion of this reabsorption takes place in the proximal tubule, but the final adjustment is achieved by the cells of distal tubules and collecting ducts. When the need for sodiuin by the body increases, several mechanisms such as decreased arterial volume, low blood pressure, decreased sodium at distal tubular exchange site, low plasma levels of sodium alert kidney. In response, specialized tissue of renal cortex release renin in the blood. Renin converts pro-hornlolie angiotensinogen secreted by liver to angiotensin TI. This, in turn, stimulates the adrenal cortex to produce aldosterone, which increases sodium re-absorption. The accompanying water retention helps, lo normalize the arterial volume thereby suppressing further renin production.

You must remember here that the regulation of chloride is achieved indirectly through sodium regulation. We need to read further to understand the details of potassium.

As observed for sodium, the maintenance of K balance also depends on the kidney. Unlike sodium, the transport of K is bi-directional during the passage of the filtrate through nephron. In the proximal tubule and loop of Henle, major portion of filtered K is reabsorbed. In the distal tubule, it can be reabsorbed from the filtrate or can be secreted into it depending on the body's need. Aldosterone acts reciprocally on Na and K. You have just seen that this hormone stimulates Na reabsorption, but it accelerates the secretion of K and thus increases its excretion. Other factors that increase K excretion are increased serum K^+ concentration and alkaline pH.

You may find it useful to refer to the Unit on 'Kidneys' in the Applied Physiology (MFN-001) Course to know the details of mechanism involved in re-absorption of sodium and secretion of K.

It is important to note that body's ability to conserve Na by restricting loss in the urine is more efficient than its ability to conserve K. Also, sodium is absorbed more efficiently from the gastrointestinal than K. Therefore, K deficiency will appear before sodium deficiency, However, dietary deficiency of these minerals does not normally occur. Deficiency is more commonly caused by vomiting and diarrhoea, which results in excessive loss of these electrolytes.

You may have come across the messages that convey the significance of promptly replenishing the electrolyte losses such as those associated with acute dirrhoea, vomiting, profuse sweating etc. Why is it important to replenish the lost reserves? This is perhaps in view of the fact that these electrolytes perform some very critical functions in the body. Our subsequent discussion highlights some of the salient functions.

Functions

So far you have learnt that most minerals participate in important functions of body as they support the activity of specific enzymes. In striking contrast to these, Na^+ and K^+ mostly function by changing their location i.e. by passing from one side of the plasma membrane to other. These electrolytes are involved in number of functions as enumerated herewith.

- These electrolytes are required for maintenance of total body water and water .balance.
- They are major determinants of osmotic pressure and electrolyte balance.
- They are involved in the maintenance of acid–base balance.
- They are major determinants of membrane potential. As you know that sodium is present in higher concentration out side the cell while K within the cell. This intracellular/extracellular difference in their concentration is responsible for the electrical potential gradient across membranes of all cells with nerve and muscle cells having highest gradients. This is critical in signal transmission across the nerve cells, muscle contraction and relaxation, synaptic transmission.
- They **are** required for the transport of glucose, amino acids within enterocyte.

The plasma membrane enzyme Na^+/K^+-ATPase is important for many functions such as water balance, membrane potentials and transport of nutrients.

In addition to the above functions, potassium is required for normal growth. Early experiments in intact cells have demonstrated a linear relation between intracellular potassium concentration and cell growth and incorporation of amino acids into protein. Sodium is involved in the formation of mineral apatite of bone while chloride is a constituent of gastric juice.

Next, we shall proceed over to the states of deficiencies and excess for these electrolytes.

Deficiency and Excess of Electrolytes

The symptoms associated with deficiency and excess intake of each of the three electrolytes is described in this section. We will begin with the hypo and hypernatremic states associated with sodium levels in the body.

Hyponatremia and Hypernatremia: Serum concentration of sodium is normally regulated within the range of 135 to 145 milimole per litre (mM/L). *Hyponatremia* is defined as a *Na level* ***under*** *130 mM/L.* When plasma Na level falls below 120 mM/L, symptoms such as headache, confusion, seizures and coma can occur. Hyponatrernia can arise from shift of water from cells to extracellular compartment, which is induced by an increase in solutes in plasma for example increased plasma glucose in diabetes can result in the shift of water from ICF to ECF, diluting the Na concentration. Hyponatremia is also induced by renal failure when kidney's impaired ability to excrete waste products results in build up of solutes in plasma. It can also occur from an overall decrease in body, Na, as occurs during diarrhoea and vomiting. Rare instances of hyponatremic dehydration have been reported in sports persons rehydrated only with water.

Hypernatremia occurs less commonly and is defined as *serum sodium level above 145 mM/L.* The initial symptoms include irritability, lethargy and restlessness. Seizures and death may occur when plasma levels rise above 160 mM/L.

Hypernatremia occurs with loss of water that is disproportionately greater than sodium and is associated with excessive sweating and hyperventilation. It can also occur when thirst mechanism is impaired because of damage to hypothalamus.

Next is discussed the states of potassium deficiency and excess.

Hypokalemia and *Hyperkalemia:* Normal serum *K* ranges from 3.5-5 mM/L. *Hypokalemia* or *low plasma* K *levels* can occur with a net shift of K from the plasma to the cells. This shift can occur in alkalosis. Overall depletion of body's K, which occurs in vomiting, prolonged fasting can also result in this shift. Mild hypokalemia results in weakness and muscle cramps and can cause arrhythmias in patients with heart diseases. Serve hypokalemia (<2.5 mM/L of K) can result in paralysis.

Hyperkalemia occurs when serum K levels are greater than 5 m M/L. High plasma K results in cardiac arrhythmias. A K level of 8.0 m M/L can cause cardiac arrest and death. Hyperkalemia can occur in severe acidosis when the activity of Na^+/K^+-ATPase is inhibited resulting in redistribution of K. It can also occur in severe kidney diseases where ability to excrete K is impaired especially if K consumption is not restricted and patient is experiencing tissue or RBC breakdown.

So then we have reviewed the deficiency symptoms and those linked with excess intake of these electrolytes. As for the recommendations for these electrolytes, no specific recommendations are made.

With this, we end our study of sodium, potassium and chloride.

So far we have learnt about the general and specific properties of several minerals. It is clear from the discussions above that several factors influence the metabolism of these minerals. Let us learn about this aspect in little more detail.

9.8 INTERACTIONS OF MACROMINERALS WITH OTHER NUTRIENTS

Various nutrients interact with minerals thereby affecting their bioavailability. These interactions occur at different sites in the body including gastrointestinal tract, during transport, at the level of storage or in the kidneys.

Most of the minerals interact with other nutrients in the intestine which either increase or reduce their absorption. These interactions which occur in the gastrointestinal tract have been covered for Ca, P, and Mg earlier under the section on absorption. The interactions which occur at other sites are briefly enumerated herewith.

- Calcium excretion through kidneys has been shown to be influenced by the levels of other minerals. Increased potassium (K) reduces urinary loss of Ca, thereby conserving the mineral. On the other hand, sodium load (100 mmol/ or 2.3 g/day) increase urinary Ca excretion. In post menopausal women urinary sodium excretion was negatively correlated which changes in hip bone density.
- Although increased phosphorous level reduces urinary losses of Ca, animal studies have indicated that low Ca : P ratios lead to progressive bone loss due to phosphorus induced stimulation of PTH release.

Ca and Mg interact at the level of kidneys. Both minerals use overlapping transport systems in the kidney and thus complete with each other for reabsorption.

- Mg may mimic Ca by binding to calcium binding sites. The ratio of calcium and magnesium has been shown to affect muscle contraction. Magnesium may compete with Ca for non-specific sites on troponin C and myosin.

  Normally Ca binding initiates acetyl choline release and smooth muscle contraction. However, binding of Mg prevents Ca binding and inhibits its contraction.

- In blood coagulation, Ca and Mg are antagonistic, with Ca promoting the process and magnesium inhibiting it.

  A close relationship also exists between Mg and K. Mg appears to be necessary for the function of Na^+/K^+ -ATPase. Therefore, deficiency of Mg would lead to impaired pumping of sodium out of the cell and the movement of potassium into the cell.

Thus, above discussion emphasizes the need of consuming diets containing appropriate amounts oi all the nutrients. Prolonged use of a nutrient supplement or fortification with a single nutrient can offset the balance thereby affecting the bioavailability and physiological functions of nutrients.

In this unit, detailed discussions have been carried out for various macro minerals. We shall continue with further discussions on other nutrients such as iron, zinc, copper and selenium in the next unit. Now try to attempt the check your progress exercise 2 to make your concepts clear.

Check Your Progress Exercise 2

1) Name the following:

   a) Most abundant intracellular mineral .....

   b) Most: abundant extracellular mineral .....

   c) Most important mineral in the bone .....

2) Enumerate the key functions of electrolytes.

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   .....

3) Do a market survey and list all the processed foods which should be avoided for a sodium restricted diet.

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   .....

9.9 LET US SUM UP

In this unit, we learnt about calcium, phosphorous, magnesium sodium, potassium and chloride which are the major macro minerals required by our body. All these macro minerals constitute an important part of our daily diet and perform both structural and metabolic functions in the body. Most minerals support the activity of specific enzymes and are thus involved in catalytic function. However, Na and K majorly function by

changing their location i.e. from one side of plasma membrane to other. Concentrations of most minerals especially in the plasma are maintained within a narrow range. Regulation occurs either at the level of absorption or excretion or storage. Also, these minerals interact with each other and other nutrients thereby influencing their bioavailability. Therefore, there is a need to consume diets containing appropriate amounts of all the nutrients.

9.10 GLOSSARY

Achlorhydric patients : patient with a lack of hydrochloric acid in the stomach.

Enterocytes : is a type of epithelial cell of the superficial layer of the small and large intestine tissue.

Wydroxyapatite : it is the major component, and an essential ingredient, of normal bone and teeth. It is hydroxyapatite that makes up bone mineral and the matrix of teeth.

Resorption : dissolution of bone calcium.

Vasodilation : is the process where blood vessels in the body become wider following the relaxation of the smooth muscle in the vessel wall.

9.11 ANSWERS TO CHECK YOUR PROGRESS EXERCISES

Check Your Progress Exercise 1

1) Macro minerals such as calcium are required in amounts greater than 100 mg per day. On the other hand, requirement of micro minerals such as selenium varies from a few milligrams to micrograms per day. Macro minerals contribute significantly towards the formation of body structure whereas micro minerals generally help in performing these or other metabolic functions.

2) a) 3 hormones viz., parathyroid hormone (PTH), calcitriol ($1,25\ (OH)_2\ D_3$) and calcitonin.

b) Meat, fish poultry, egg, milk and its products, nuts, legumes and cereals,

c) Calcification of non-skeletal tissues which may lead to organ damage resulting in hypothyroidism/end stage renal disease.

3) a) Elderly are more prone to fractures due to osteoporosis, There is a sharp decline in the bone mass with advancing age due to its association with oestrogen and physical inactivity.

b) Plasma calcium level is not a good indicator of calcium status because of the body's feedback mechanism which promotes bone mineral accretion during low calcium levels in plasma. Thus bone mineral density is a more reliable indicator.

Check Your Progress Exercise 2

1) a) Potassium

b) Sodium

c) Calcium

2) Important functions of electrolytes include:

- These electrolytes are required for maintenance of total body water and water balance.
- They are major determinants of osmotic pressure and electrolyte balance.
- They are involved in the maintenance of acid–base balance.
- They are major determinants of membrane potential.

3) Answer this question on your own based on a market survey to identify the presence of salt, sodium chloride or certain additives such as sodium citrate/ sodium benzoate in packaged foods. For eg. salt/sodium chloride is' present in potato chips, ketchups. Now read the label of canned foods, squashes etc. to identify if sodium is present.