body functions are impaired. The functions and routes of metabolism for some micro elements are well established both in animals and humans while for others, the data are available only from animal studies. They normally function as a cation (ion with a positive charge) complexed with organic ligands or chelators. Proteins are the most important chelators. Besides these, porphyrin (the ring structure present in haemoglobin) and corrins (the ring structure in vitamin B_{12}) are other important chelators. As components of enzymes and proteins, these minerals frequently participate in redox reactions (reactions which involve the transfer of electrons) with the metal often functioning as the electron carrier. However, minerals such as zinc and manganese along with macro elements calcium and magnesium, perform non-redox functions in proteins and enzymes. Since many of the micro minerals share common mechanism for absorption, they compete with each other for absorption in the small intestine. Thus, excess of one micro element can aggravate the deficiency of another. Iron and zinc are the best known examples.

With this basic overview, we shall get to know about micro minerals in greater detail in the subsequent section(s). We begin our study with iron.

10.3 IRON

Iron was a familiar metal even in the ancient civilization. In India, iron implements made their appearance in between 1300-1000 BC and in due course, iron was used in a variety of cookery utensils. The presence of leached iron, especially when acidic foods were cooked in such utensils, was considered to be a significant contributor to dietary iron. The most important clinical application of iron was described in the 17th century, for treating "chlorosis"–a condition that resulted from severe iron deficiency in adolescent females in whom the dietary iron intake was only 4-3 mg/day as against the average iron content of 8-11 mg/day in normal persons. Major aspects of iron metabolism were elucidated by 1960 and today iron is one of the most investigated minerals in nutrition. Let us read further to understand the importance of iron in maintaining good health.

We all associate iron with its presence in blood and that its deficiency results in low haemoglobin levels and hence anaemia. But is iron present only in blood? Of course not. In our subsequent discussion, we will learn about the iron stores in the human body.

Total Body Iron

In humans, the total quantity of iron in the body varies with haemoglobin concentration, body weight, gender and the amount of iron stored in various tissues. Approximate distribution of body iron is shown in Table 10.1.

Table 10.1: Distribution of body iron in different compartments

Compartment	Iron Content (mg)	Total Body Iron %
Haemoglobin Iron	2000	67
Storage Iron	Varies from 200-1000	627
Tissue Iron: Myoglobin	130	3.5
Enzyme Iron	8	0.2
Other-transport Iron & labile pool	83	2.28

Source: Modern Nutrition in Health and Disease 8th Ed., 1994.

You may have observed in Table 10.1 that maximum amount of iron is incorporated in haemoglobin. The amount of storage iron shall depend upon the dietary iron consumed and its bioavailability. It would be interesting to note here that iron can

exist in a number of oxidation states ranging from Fe^{2-} to Fe^{6+}. You must also remember that in the human body and food, it occurs generally as ferric (Fe^{3+}) and ferrous (Fe^{2+}) iron. We have so far discussed about the presence of iron in the body. Let us now quickly find out about the presence of iron in food i.e. learn about the food sources of iron.

Food Sources

Iron is found in foods in one of the two forms i.e. *haem* or *non-haem*. In the human diet, the primary sources of haem iron are the haemoglobin and myoglobin from consumption of meat, poultry and fish whereas non-haem iron is obtained from cereals, pulses, legumes, fruits and vegetables. Dietary non-haem iron accounts for about 85% of the total iron intake even among non-vegetarians. The good plant and animal food sources of iron are shown in the Table 10.2 (a) and (b).

Table 10.2 (a): Sources of haem iron and their content (mg)

Haem Iron Sources	Fe Content
Chicken liver	7.5
Chicken	1.1
Eggs	1.1
Salmon	1.0

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, NIN, 1989.

Table 10.2(b): Sources of non-haem iron and their content (mg/100)

Non-haem Iron Sources	Fe Content
Dried apricots	5.5
Almonds	1.3
Raisins	3.5
Soybeans, Tofu	1.9
Spinach	3.1
Wheat germ	0.9
Kidney beans	2.5
Baked beans	1.5
Broccoli	0.5
Lentils	6.0

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, NIN, 1989.

Let us read further to find out as to how dietary iron is digested, absorbed, transported, utilized and excreted from the human system or in other words, how are adequate levels of iron maintained in different body compartments.

Metabolism of Iron

In this sub-section, we will study how body gets its iron supply, how iron is transported and utilized by the various tissues and how iron balance is maintained.

Like other minerals, we obtain iron from the diet, which is absorbed from the gastrointestinal tract. A unique feature of iron metabolism is that the body re-utilizes quantitatively the iron released from the degradation of erythrocytes, with very little being excreted. Hence, it is very frequently mentioned that once iron enters the body, the body holds on to it tenaciously. We will first learn how dietary iron is absorbed and then review how the iron is re-utilized.

Absorption of Iron

Before it can be absorbed, iron whether it is in the form of haem or non-haem. must be released from the food matrices where it is bond with other constituents. ***Proteases*** (the enzyme) in the stomach and small intestine hydrolyze haem iron from the globin portion of haemoglobin or myoglobin. In the case of non-haem iron, gastric secretion including HCl and pepsin aid its release from food components. Most non-haem iron is present in the ferric form which is reduced to ferrous form in the acidic environment of the stomach. However, as the ferrous iron passes into the small intestine (alkaline pH), some Fe^{2+} may be oxidized to become ferric iron. Following its liberation from food components, absorption takes place. Like other minerals, iron is also absorbed in duodenum and upper jejunum. The process of absorption is divided into three phases:

i) Iron uptake by enterocytes (epithelial cell of the superficial layer of the small and large intestine tissue)

ii) Intra enterocyte transport

iii) Storage and extra enterocyte transport.

The mechanism of absorption differs for non-haem and haem iron and therefore they will be dealt separately. Let us have a look at the non-haem iron absorption first.

a) ***Mechanism of Non-haem Iron Absorption***

We will discuss all the three phases one by one.

i) ***Uptake of iron by enterocytes:*** Ferrous iron traverses the brush border of the intestine better than the ferric iron. The mechanism of absorption of the latter is not clear but it is postulated that it binds to luminal binding proteins. Mucin, a small protein made in the intestinal cells and released into the gastrointestinal tract, is thought to facilitate iron absorption. It binds multiple Fe^{3+} ions at an acidic pH and maintains its solubility even in alkaline pH and thus aids in its absorption. After traversing the brush border, iron binds to the receptor on the luminal surface of enterocyte and is transported inside the cell.

ii) ***Intra enterocyte transport: In*** the enterocyte, the absorbed iron can have one of the following metabolic fates:

- transported through the enterocyte into the blood, and
- stored in the enterocyte for future use or elimination.

Iron is transported through the enterocyte to the baso-lateral membrane by iron binding protein – *mobilferrin*. Mobilferrin can also bind to Ca, Cu and Zn. The multiple metal ion-binding properties of mobilferrin may be partially responsible for interactions. between these minerals at absorptive surface.

The iron which is not transported across the cell for release is stored as ***ferritin*** in mucosal cells. If required for the body, it is released for transport. If not needed, the iron remains as ferritin and is excreted when mucosal cells are sloughed off in the lumen, Thus, ferritin in the enterocyte acts as an 'iron sink', trapping excess iron and removing it via intestinal excretion.

iii) ***Extra enterocyte transfer:*** Little is known about iron transport across the baso-lateral membrane. After crossing the baso-lateral membrane, it binds to plasma transport protein ***transferrin.*** Iron is oxidized before it can bind to transfemn. This is brought about by ***ceruloplasmin,*** a Cu-containing protein. The process has been depicted in Figure 10.1.

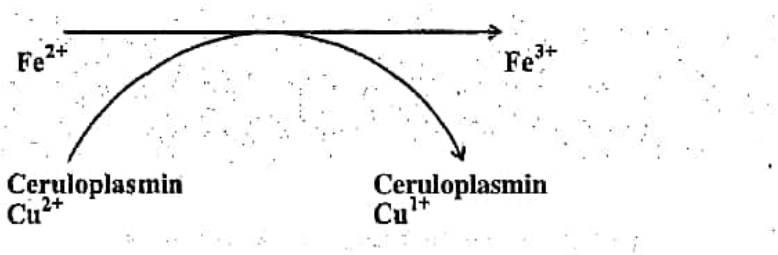


Figure 10.1: Oxidation of iron

Next, we shall review the mechanism of absorption of haem iron.

b) *Mechanism of Absorption of Haem Iron*

Haem iron is soluble in the alkaline environment of the intestine. It binds to the receptor on the enterocytes and is internalized. After entering the mucosal cell, haem is degraded to iron, carbon monoxide and bilirubin IXa by the enzyme *haemeoxygenase*. The liberated iron is then treated in the same manner as is the non-haem iron.

We have read in the previous units that whatever may be the quantity of a particular nutrient that we may consume, the entire amount may not get digested and absorbed (bioavailable) due to varied reasons. Let us see what factors affect the bioavailability of dietary iron.

Factors affecting Absorption of Dietary Iron

Haem iron is more bioavailable than non-haem iron because it is absorbed intact as a soluble complex by endocytosis (process whereby cells absorb material, molecules such as proteins, from outside by engulfing it with their cell membrane). Non-haem iron, on the other hand, forms insoluble complexes with many components concurrently present in the diet, rendering the iron unavailable for mucosal uptake. The absorption of iron also depends on the iron status of the individual and on the availability of an iron-binding mucosal transport protein (transferrin) to facilitate the uptake from the intestines.

There are mainly four factors that determine iron bioavailability/ absorption from the diet. These include:

i) Form of iron; whether haem or non-haem

ii) Solubility; specially of the non-haem iron compounds

iii) Other dietary factors; inhibitors and enhancers

iv) Iron status of the individual

Our subsequent discussions will elaborate upon each of these aspects.

i) *Form of Iron:* We have read earlier that iron in foods occurs either as haem or non-haem iron. Haem iron comprises of iron in combination with porphyrins and is found only in the flesh foods in the form of haemoglobin and myoglobin. Muscle meats are therefore good sources of haem iron. Haem iron is absorbed to a much greater extent than non-haem. Haem iron absorption is generally 2-3-fold higher than non-haem iron absorption. The average absorption of haem iron from meat-containing meals is about 25%. The absorption of haem iron can vary from about 40% during iron deficiency to about 10% during iron repletion. Haem iron can be degraded and converted to non-haem iron if foods are cooked at a high temperature for too long. Iron absorption is not affected by other dietary factors except calcium which has been shown to depress haem iron absorption. In addition to providing higher bioavailable iron, haem iron compounds also enhance non-haem iron absorption. Further, non-haem iron absorption in healthy adults may vary from less than 1% to about 0% depending on the composition of the diet,

The next factor that is being discussed is the solubility of the iron/its complex with other substances.

ii) **Solubility:** Solubility is crucial for non-haem iron absorption as the inorganic iron salts have to be solubilized in the intestine for the iron to be taken up by the muscosal cells. The acidic pH of the stomach makes iron soluble. However, as the chyme passes into the small intestine, the rising pH tends to precipitate iron as femc hydroxide complexes, The presence of ascorbic acid and other organic acids in the small intestine solubilize to chelate the iron so that it can be absorbed. Ferrous salts are more soluble than ferric salts and are therefore better absorbed.

iii) *Inhibitors and Enhancers: Phytates* and *fibre* from whole grain cereals, *tannins* and *polyphenols* in tea, *oxalates* in green leafy vegetables like spinach and excess *calcium* taken as supplements can all *depress non-haem iron absorption* significantly, by forming insoluble components. The Indian vegetarian diet consisting predominantly of cereals and pulses, high in phytates, has a low iron bioavailability. This is further compromised when tea is drunk with a meal, as polyphenols in tea depress iron absorption. Iron absorption from wheat has been reported to be *5%*. However, when tea is taken with a breakfast meal comprising of wheat chapattis and potato vegetable, the reported absorption has been only 1.8%. Ragi balls or sorghum breakfast with potato vegetable and tea resulted in only 0.8-0.9% absorption of iron.

On the contrary, *ascorbic acid* is *a potent enhancer* of iron absorption. Addition of orange juice containing 40-50 mg ascorbic acid to a breakfast meal consisting of bread, eggs and tea was found to increase iron absorption from 3.7% to 10%. Thus, ascorbic acid can counter the inhibitory effect of tannins or phytates, producing a 2-3 fold increase in iron absorption.

Thus, ascorbic acid can enhance iron absorption in a number of ways. Firstly, it reduces insoluble ferric iron to soluble ferrous iron; secondly, ascorbic acid forms low molecular weight chelates with iron that remain soluble in the intestine; thirdly, ascorbic acid-iron chelates preferentially release the iron for absorption to the brush border. Together, these mechanisms ensure that dietary iron is well absorbed in the presence of ascorbic acid.

Other factors known to enhance iron absorption are meat and flesh foods and some amino acids such as cysteine.

The best way to increase bioavailability of iron in Indian vegetarian diet is to consume adequate amounts of ascorbic acid rich fruits and vegetables with the meals, reduce phytate content by appropriate home levels processes such as gemination and fermentation and avoid drinking tea with the meals.

Another factor which may determine the absorption of iron is the existing iron status of the individual. This is particularly relevant with respect to iron deficiency anaemia.

iv) *Iron Status of the Individual:* Lastly, iron status of the individual is a floury determinant of how much iron is absorbed. On a mixed diet with some haem iron, the overall absorption may approximate to 10% in normal subjects while it is about 20% in iron deficient subjects.

Table 10.3 lists the currently known dietary factors affecting iron absorption.

Table 10.3: Dietary factors affecting iron absorption

Increase Absorption	Decrease Absorption
• Gastric Acidity	• Increased intestinal motility
• Ascorbic Acid	• Phytates and oralates
• Certain organic acids like citric, lactic and tartaric acid	• Iron-binding phenolic compounds such as ferrous pyrophosphate, ferrous citrate
• Animal proteins such as meat, fish, poultry	• Calcium, Phosphorus and Magnesium
• Sugars – Fructose, sorbitol	• Zinc, Manganese and Copper
• Physiological factors–pregnancy and growth	• Tannic acid in coffee and tea
• Depleted iron status	• High Iron status
	• Antacids • Achlorhydria, Hypochlorhydria
	• Poor fat digestion

So far we have discussed about the various aspects of iron absorption. However, it was also mentioned that once iron gets absorbed, it is utilized judiciously again and again by our body. What is the mechanism that regulates iron balance and absorption? Let us understand about 'it in detail.

Iron Balance and Regulation of Iron Absorption

The body has three unique mechanisms for maintaining iron balance.

The first is the continuous *reutilization of iron* from catabolized erythrocytes in the body. When an erythrocyte dies after about 120 days, it is usually degraded by the macrophages of the reticular endothelium. The iron is released and delivered to transferrin in the plasma, which brings the iron back to red blood cell precursors in the bone marrow or to other cells in different tissues. Uptake and distribution of iron in the body is regulated by the synthesis of transferrin receptors on the cell surface. This system for internal iron transport not only controls the rate of flow of iron to different tissues according to their needs, but also effectively prevents the appearance of free iron and the formation of free radicals in the circulation.

The re-utilization of iron is a highly significant process. As mentioned earlier, the red blood cells (erythrocytes) contain two thirds of the total body iron. If 1/120th of this is to be degraded daily, (note: life span of erythrocytes is 120 days) it results in the release of about 20 mg of iron daily within the body. Almost all of this is re-utilized for the synthesis of new haelnoglobin and erythrocytes. Only an extremely small proportion i.e., about 1 mg is lost from the body to be replaced by dietary iron. The amount of iron released from erythrocytes and re-utilized for new haemoglobin is termed as ***iron turnover*** in the body.

The second mechanism involves access to the specific storage protein, ***ferritin***.. This protein stores iron in periods of relatively low need and releases it to meet excessive iron demands. This iron reservoir is especially important in the third trimester of pregnancy.

The third mechanism involves the regulation of absorption of iron from the intestines; decreasing body iron stores trigger increased iron absorption and increasing iron stores trigger decreased iron absorption. Iron absorption decreases until equilibrium is established between absorption and requirement,

Now we shall discuss the transport and storage of absorbed dietary iron in our body.

Transport and Storage

You have seen that transferrin binds both newly absorbed iron and iron released after degradation of haemoglobin. Transferrin is a glycoprotein and has two binding sites for Fe^{3+}. It acts as an iron transport protein. Normally, in plasma it is one-third saturated with ferric ions. It distributes iron throughout the body to wherever it is needed, mostly to erythrocyte precursors in the bone marrow. In iron deficiency, transferrin saturation is reduced while in iron overload, tansferrin saturation gets increased.

Any absorbed iron in excess of body needs is stored in the liver, in two forms, as *ferritin* and *haemosiderin*. Ferritin and haemosiderin are the two major iron storage proteins. The ratio of these two proteins in the liver varies according to the level of iron stored, with ferritin predominating at lower iron concentrations and haemosiderin at higher concentrations. Iron is released from these stores in times of need more readily from ferritin than haemosiderin.

Binding of iron by protein during storage and transport serves as a defense mechanism. How? If iron ions are left unbound, the redox activity of iron can lead to the

generation of harmful free radicals that can cause damage to the cells and their membranes.

We have been reading that once iron is absorbed, our body tries to use it conservatively and re-utilizes it again and again. What would happen then, if iron is consumed in excess of our requirements? Further, the iron absorption need not always be complete. Unabsorbed iron would get excreted. Let us read how iron gets excreted from the body.

Excretion

Our body has a limited capacity to excrete iron once it has been absorbed. Daily losses in adult man are between 0.9 to 1.05 mg. About 0.08 mg is lost via urine, 0.2 mg via skin,and remaining in the faeces. Women in the reproductive age lose more iron owing to menstrual cycles.

Iron is unique among the minerals, that once absorbed the body holds onto it, and therefore, major regulation of iron balance is through absorption of iron rather than through excretion. The percentage of iron absorbed can vary from less than 1% to more than 50%, depending on the food eaten and the response of the regulatory mechanisms that reflects body's physiological need for iron. However, this regulatory mechanism is not perfect across the entire range of intakes.

Next, we shall discuss how iron is taken up by different tissues to perform various functions in the body.

Iron Uptake by Cells and its Functions

Iron participates in a large number of biochemical reactions. However, for iron to perform any function, it first needs to be taken up by the cells. Let us then first review iron uptake by cells.

Cell membranes contain a protein specific for binding transferrin called '*transferrin* receptor'. Transferrin containing two ferric ions, binds to this receptor. Thereafter, iron-transfenin-transferrin receptor complex is internalized by endoyctosis. Within the cell, iron is released from transferrin.

It has been shown that intracellular iron concentration more or less remains constant. This intracellular iron homeostasis is maintained by regulating the synthesis and action of proteins involved in the iron acquisition, utilization and storage. When intracellular iron is scarce, cell needs to increase its iron concentration. This is achieved by acquisition of plasma iron and mobilization of storage iron. Also, there is a need to prioritize utilization of iron so that iron is preferentially available for the synthesis of life sustaining iron-containing proteins. Therefore, whenever the intracellular iron concentration is low, the number of transferrin receptors on the cell increase. Further, it is postulated that iron concentration also regulates the synthesis of *apoferritin* and *δ-aminolevulinic acid synthase.* The latter is the key enzyme for haem synthesis.

Now that we have been acquainted to the mechanism involved in iron uptake by cells, let us focus on the functions of iron.

Iron has several vital functions in the body. It serves as a carrier of oxygen to the tissues from the lungs by red blood cell haemoglobin, as a transport medium for electrons within cells, and as an integrated part of important enzyme systems in various tissues. The general classification of the reactions in which iron is involved includes:

- Oxygen transport and storage
- Electron transfer
- Substrate oxidation–reduction

Four major classes of iron containing proteins carry out these reactions in the mammalian system. These are illustrated in Figure 10.2.

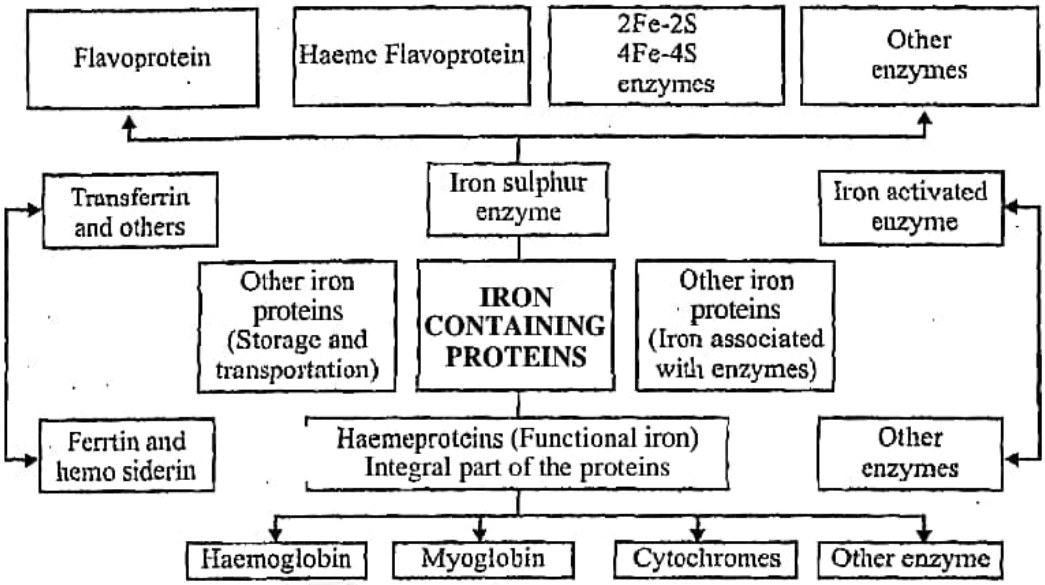


Figure 10.2: Classification of major mammalian iron containing proteins

Source: Beard and Dauson, 1997

Several iron-containing enzymes, the cytochromes, have one haem group and one globin protein chain. These enzymes act as electron carriers within the cell and their structures do not permit reversible loading and unloading of oxygen. Their role in the oxidative metabolism is to transfer energy within the cell and specifically in the mitochondria. Other key functions for the iron-containing enzymes (e.g. cytochrome P450) include the synthesis of steroid hormones and bile acids; detoxification of foreign substances in the liver; and signal controlling in some neurotransmitters, such as the dopamine and serotonin systems in the brain.

As a component of cytochromes and other enzymes of electron transport chain, it is critical for conversion of food into ATP. Iron-containing molecules ensure that macromolecules like carbohydrates and fats are oxidized to provide the energy necessary for all physiological processes and movements.

Iron is a component of many other tissue enzymes required for immune system functioning. Non-haem iron proteins, as we know, are responsible for a wide range of functions such as enzymes methane mono-oxygenase (oxidizes methane to methanol) and ribonucleotide reductase (reduces ribose to deoxyribose; DNA biosynthesis).

As a part of haemoglobin, iron is required for the transport of oxygen, to all cells in the body. Thus, haemoglobin is critical for cell respiration. Most of the iron in the body is present in the erythrocytes as haemoglobin, a molecule composed of four units, each containing one haem group and one protein chain. The structure of haemoglobin allows it to be fully loaded with oxygen in the lungs and partially unloaded in the tissues (e.g. in the muscles). The iron-containing oxygen storage protein in the muscles, myoglobin, is similar in structure to haemoglobin but has only one haem unit and one globin chain. As myoglobin, iron functions as a ready source of oxygen to the muscles.

Iron is thus crucial for the survival, growth and normal functioning of the human system. Let us now read about the consequences of deficiency and iron overload in the body.

Deficiency and Iron Overload

In the following discussion, we shall cover both the deficiency and the consequences of iron overload. We shall begin with iron deficiency.

Deficiency of Iron

Iron deficiency and *iron deficiency anaemia* are often incorrectly used as synonyms. Iron deficiency is defined as *a haemoglobin concentration below the optimum value in an individual,* whereas iron deficiency anaemia implies that *the haemoglobin concentration is below the 95th percentile of the distribution of haemoglobin concentration in a population* (disregarding effects of altitude, age and sex, etc. on haemoglobin concentration). Normally, iron deficiency anaemia is defined in terms of lower then normal blood haemoglobin levels and at least two of the following three: i) reduced serum ferritin, ii) increased erythrocyte protoporphyrin, and iii) increased transferrin receptors. Iron deficiency is one of the most prevalent nutritional deficiencies in the world today. It is estimated that 2 billion people worldwide suffer from different degrees of iron deficiency, about half of them, manifesting iron deficiency anaemia.

The progression from adequate iron status to iron deficiency anaemia develops in three overlapping stages. The *first stage* is depletion of storage iron with serum ferritin levels starting to decline. However, the transferrin saturation, erythrocyte protoporphyrin and haemoglobin are within normal limits. As iron stores get increasingly depleted, iron deficiency develops which is the *second stage.* During this stage, in addition to low serum ferritin levels, transferrin saturation is also reduced and erythrocyte protoporphyrin is elevated. Haemoglobin may be normal. Eventually when iron deficiency progresses to anaemia, haemoglobin levels start declining; this is the *third and final stage* of iron deficiency.

The functional effects of iron deficiency anaemia result from both a reduction in circulating haemoglobin and a reduction in iron-containing enzymes and myoglobin. These include:

- fatigue, restlessness and impaired work performance,
- disturbance in thermoregulation,
- impairment of certain key steps in immune response,
- adverse effects on psychomotor and mental development particularly in children, and
- increased maternal and perinatal mortality and morbidity .

Studies in animals have clearly shown a relationship between iron deficiency and brain functions. Several structures in the brain have high iron content. The observation that the lower iron content of the brain in iron-deficient growing rats cannot be increased by giving iron at a later date, strongly suggests that the supply of iron to brain cells takes place during an early phase of brain development and that, as such, early iron deficiency may lead to irreparable damage to brain cells. In humans, about 10% of brain-iron is present at birth; at the age of 10 years, the brain has only reached half its normal iron content, and optimal amounts are first reached between the ages of 20 and 30 years. Several groups have demonstrated a relationship between iron deficiency and attention, memory and learning in infants and small children. In the most recent well-controlled studies, no effect was noted from the administration of iron.

Iron deficiency also negatively influences the normal defence systems against infections. Several studies have observed a reduction in physical working capacity in human populations with longstanding iron deficiency, and demonstrated an improvement in working capacity in these populations after iron administration. Well-controlled studies in adolescent girls show that iron-deficiency without anaemia is associated with reduced physical endurance and changes in mood and ability to concentrate.

Considering the ill-effects of iron deficiency, preventing this problem is crucial. Populations most at-risk for iron deficiency are infants, children, adolescents and women of childbearing age, especially pregnant women. The weaning period in infants is especially critical because of the very high iron requirement needed in relation to energy requirement. Let us then focus our attention on prevention of iron deficiency.

Prevention of Iron Deficiency

Iron deficiency anaemia accounts for approximately one-half or more of all the anaemia's seen world wide. Iron deficiency without anaemia affects a large segment of the populations, as many as with anaemia. Thus, 70% or more of the pre-school children, 90% or more of pregnant women and adolescent girls suffer from either iron deficiency or iron deficiency anaemia in India. The serious functional effects of iron deficiency anaemia on learning, cognition and physical performance in children and productivity in adults, as well as, increased maternal and pre-natal mortality in pregnant women make it imperative to prevent and or treat iron deficiency as a priority.

There is a major National programme, the *National Nutritional Anaemia Control Programme* that aims to prevent and treat anaemia in pregnant women using a public health approach. Iron (100 mg elemental iron) and folic acid (0.5 mg) in the form of tablets are provided to all pregnant women for 100 days during a pregnancy through the ICDS.

Severely anaemic women are given two tablets a day for 100 days as a treatment. Medicinal iron in a suitable form proves useful in treating iron deficiency at individual levels. Long-term prevention of iron deficiency must depend on improving the bio-availability of iron and increasing the iron content of the diets. Studies have shown that consumption of fruits rich in ascorbic acid such as guavas with major meals can improve haemoglobin levels. Drinking tea with meals should be avoided. At least a gap of ½-2 hours is needed between a meal and tea for better iron absorption.

While the deficiency of iron is a common health problem; it is important to consider the causes of this problem. Nutritional iron deficiency implies that the diet cannot supply enough iron to coves the body's physiological requirements for this mineral. Worldwide, this is the most common cause of iroh deficiency. In many tropical countries, infestations with hookworms lead to intestinal blood losses that in some individuals can be considerable.

Besides deficiency conditions, there can be situations (though rare) when there is excessive accumulation of iron in the body. Let us next discuss the consequences of iron toxicity.

Iron Overload/Toxicity

We have seen that absorption of iron is very effectively regulated. This prevents overload of the tissues with iron from diet/supplements in normal healthy individuals. However, an excessive body burden of iron can be produced by greater-than-normal absorption from the alimentary canal, by parenteral injection or by a combination of both. For instance, people with genetic defects develop iron overload as it occurs in *idiopathic haemochromatosis*. It is *a hereditary disorder of iron metabolism characterized by abnormally high iron absorption owing to a failure of the iron absorption control mechanism at the intestinal level.* High deposits of iron in the liver and the heart can lead to cirrhosis, hepatocellular cancer, congestive heart failure and eventual death.

African or Bantu siderosis, chronic liver disease, pancreatic insufficiency, shunt haemochromatosis and certain types of refractory anaemia have been found to be associated with iron overload. It has recently been shown that excess iron intake via

overuse of iron supplements could pose a possible health risk. Cellular and tissue injury due to free radical reactions appears to be the possible mechanism. Normally iron is bound tightly to the proteins. However, it is possible that excess iron intake permits some iron to be in a free form. Associated complications may include increased risk for bacterial infection, neoplasia, arthopathy, cardiomyopathy and endocrine dysfunction.

Next, we shall learn about the indicators of iron status in the human body. These indicators/values provide valuable information to plan the subsequent course of treatment and ensure proper rehabilitation.

Assessment of Iron Status

In view of widespread iron deficiency, it is important to have reliable and sensitive measures of iron status. Iron status can be assessed by a number of methods, which are suitable for different stages of iron deficiency. These are briefly discussed below:

i) *Serum Ferritin:* This method is indicative of iron stores. As we know, a long term negative iron balance first results in depletion of iron stores with a fall in serum ferritin levels. Plasma femtin concentration of less than 30 microgram per litre is considered indicative of iron deficiency. In normal subjects, plasma femtin averages 100 mcg/L. Values in excess of 250 mcg/L are indicative of iron overload.

ii) *Transferrin receptors:* As iron deficiency progresses into second stage, the number of transferrin receptors on the cell surface increase. Measurement of serum tranfemn receptors is thought to reflect transferrin receptors on immature red cells. Values more than 8.5 mg/L reflects iron deficiency.

iii) *Erythrocyte protoporphyrin:* In the early stages of iron. deficiency, there is accumulation of free protoporphyrin (precursor of haemoglobin). Zinc protoporphyrin is usually measured. Levels more than 40 micro mol/mol haem is associated with iron deficiency.

iv) *Transferrin saturation:* As iron deficiency progresses, there is a decline in transferrin saturation. With deficiency, transferrin saturation reduces to less than 15-16%, is indicative of iron deficiency.

v) *Haemoglobin and Haematocrit:* In the final stages of iron deficiency, anaemia occurs. Haemoglobin and haematocrit levels indicate prevalence of anaemia. Haematocrit represents that *proportion of the total blood volume that is red blood cell and is expressed as percentage (%).* Values of these two indicators, below which anaemia is considered to exist, according to age and sex is given in the Table 10.4.

Table 10.4 : Haemoglobin and haematocrit levels below which anaemia is present

Age/ Gender Group	Haemoglobin(g/l)	Haematocrit (mmol/L)
Children 6m-59m	110	6.83
Children 5-11 years	115	7.13
Children 12-14 years	120	7.45
Non-pregnant women (above 15 years of age)	120	7.45
Pregnant women	110	6.83
Men (above 15 years of age)	130	8.07

Source: WHO, 2001.

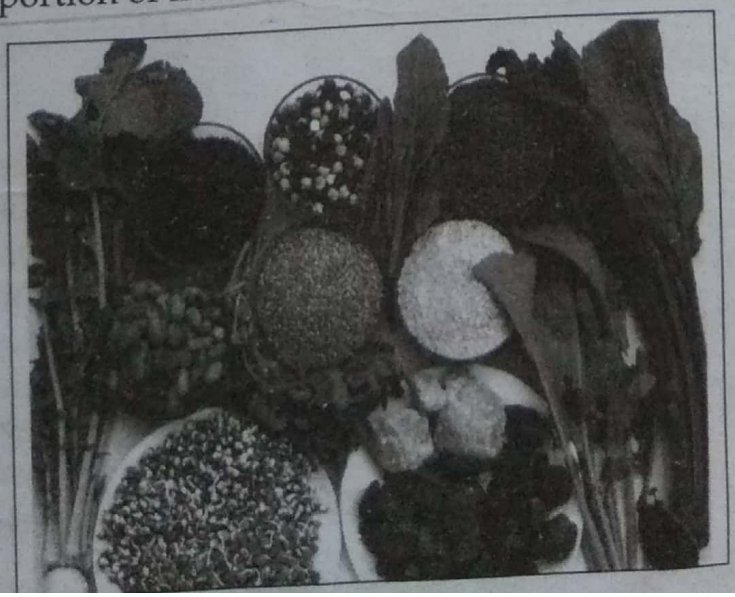
So, how much iron should be consumed in order to maintain an adequate iron nutriture? Let us read and find out.

Table 11.5: ICMR Recommended Dietary Allowances of Iron–2010

Group	Iron mg/day
Man	17
Woman	21
Pregnancy	35
Lactating	25
Infants	
0–6 months	46 µg/kg
6–12 months	05
Children	
1–3 years	09
4–6 years	13
7–9 years	16
Boys	
10–12 years	21
13–15 years	32
16–17 years	28
Girls	
10–12 years	27
13–15 years	27
16–17 years	26

SOURCES

Haeme iron from animal foods is better absorbed than nonhaeme iron present in plant sources. Liver is the best source of iron. Iron is also absorbed well from red meat like beef and lamb. Nonhaeme iron is present in cereals, millets, pulses and green leafy vegetables. Of the cereal grains, wheat and millets like bajra and ragi are very good source of iron. Phytates and oxalates present in plant foods may affect the absorption of iron by forming insoluble complexes. Inclusion in our daily diet about 50 g of green leafy vegetables which are rich in iron can meet a fair proportion of iron needs.



the greater need for iron in these cells is met by increasing the number of receptors, which regulate the inflow of iron into these cells.

Lactoferrin and lactalbumin: Although the iron content of human milk is very low, it is highly bioavailable because of the presence of milk lactoferrin, which enhances iron absorption. Infants retain more iron from human milk than from cow's milk or infant formulas because of the presence of lactoferrin in breast milk. When protein, lactalbumin, which constitutes a greater percentage of the total protein in human milk than in cow's milk may also improve iron absorption.

Recent evidences suggest that a low molecular weight human milk whey factor increases bioavailability of ferric iron. Research conducted at National Institute of Nutrition (2008–09) showed that ferric reductase activity in low molecular weight human milk fractions and provided evidences for enhanced ferric iron solubility.

Calcium: An adequate amount of calcium helps bind and remove agents such as phosphate and phytate which if not removed would combine with iron and inhibit its absorption.

Inhibiting Factors

Low gastric acidity: Decreased secretion of hydrochloric acid in the stomach, over consumption of antacids or gastric surgery can lead to decreased absorption of nonhaeme iron. The secretion of hydrochloric acid into the stomach often decreases naturally with ageing.

Increased gastric motility: Dietary fibre like hemicellulose causes reduction in absorption. Cellulose has no such effect. Fibre reduces iron absorption by increasing peristaltic movements. Foods high in fibre are also high in phytate whose absorption strongly inhibit iron absorption. Malabsorption syndrome or any disturbance that causes diarrhoea or steatorrhoea hinders iron absorption.

Phytates and oxalates: These combine with iron ions and convert iron into an insoluble form which is unavailable to the body. Phytic acid is a phosphorus containing organic acid found in whole grains, bran and soya products. Ascorbic acid in sufficient amounts can partly counter act this inhibition. Fermentation degrade phytate and increase iron absorption. Oxalic acid is an organic acid found in spinach and chocolate. They form insoluble salts with iron.

Polyphenols: These are organic compounds present in coffee, tea, cocoa and some vegetables. They are able to reduce the absorption of iron from a meal by as much as 70 per cent by their ability to form insoluble complexes with iron. Phenolic compounds having mainly galloyl groups are responsible for the inhibition of iron absorption. Drinking tea with main meals is probably important factor for iron deficiency.

Minerals: Cobalt, zinc, cadmium, copper and molybdenum are competitive absorption inhibitors for iron. Manganese and iron appear to share same absorption pathway. One which is taken in high quantity can inhibit the other. Calcium interferes with the absorption of haeme and nonhaeme iron at the mucosal cell. The practical solution to this competition is either to increase the intake of iron to increase its bioavailability or to separate the intake of calcium and iron in different meals.

Infection: Severe infections hinder iron absorption.

Nontissue Proteins: Nontissue protein sources such as milk, cheese and eggs decrease iron absorption.

Table 11.3 shows that rice based diets have better absorption of iron than wheat/millet based diet. Iron absorption is better during pregnancy, anaemia and in female adolescence.

In an Ethopian study (1993), it was found that iron pots released significantly more available iron into food than the other pots and iron availability was better for meat and vegetables than for legumes. In this study, children fed food cooked in iron pots has higher concentrations of haemoglobin than children fed food cooked in aluminium pots. Serum ferritin levels were also increased.

Using iron pots to improve haemoglobin levels is less expensive than supplementation costs and iron fortification. And also serve the whole family and might face less cultural resistance and cost less than other strategies to control anaemia. Food in villages is likely to be contaminated with iron from water, soil residues or dust. Though rice is not a good source of iron, rice flakes contain iron which is acquired from iron pounders during processing.

Sources of iron are given in the Table 11.6.

Table 11.6: Iron Content of Plant and Animal Foods

Plant foods (nonhaeme iron)	mg/100 g	Animal Foods (haeme iron)	mg/100 g
Cauliflower greens	40	Crab muscle	21
Manathakkali leaves	21	Ribbon fish fresh	14
Rice flakes	20	Herring, Indian	9
Beet greens	16	Liver sheep	6
Mint	16	Prawn	5
Paruppukeerai	15	Mackerel	5
Soyabean	10	Mutton muscle	3
Colocasia leaves	10	Sardine	3
Bengalgram roasted	10	Pomfrets black	2
Gingelly seeds	9	Pork muscle	2
Cow pea	9	Egg hen	2
Bajra	8	Shark	1
Onion stalks	7	Beef	1
Dates dried	7	Rohu	1
Rice puffed	7		

NUTRITIONAL ANAEMIA

Nutritional anaemia may be defined as the condition that results from the inability of the erythropoietic tissue to maintain a normal haemoglobin concentration on account of inadequate supply of one or more nutrients leading to reduction in the total circulating haemoglobin.

Many nutrients are involved in the process of erythropoiesis as shown in Table 11.7.

Table 11.7: Role of Nutrients in Erythropoiesis

Nutrients		Role of erythropoiesis
Proteins	1. Glycine	Bio-synthesis of porphyrin ring of haemoglobin.
	2. Histidine	Precursor of RBC constituent ergothioneine (present upto 8% in haemoglobin)
	3. Proline and Hydroxy Proline	Have same ring structure like porphyrin present in haemoglobin formation.

Micro-Minerals	4. Iron	Haemoglobin formation in RBC Required for haeme formation
	5. Copper	Helps in absorption of iron. Synthesis of non-protein haeme or globin parts of haemoglobin, helps in release of stored iron from ferritin in liver.
Vitamins	6. Vitamin E	Gives stability to RBC membrane. Protects it from lipid peroxidation.
	7. Riboflavin	Formation of RBC in bone marrow. Stimulates reticulocytosis.
Vitamins	8. Vitamin C	Increases the rate of iron absorption into tissue thus helping in the erythiopoiesis.
	9. Vitamin B_6	Helps in incorporation of iron into haemoglobin.
	10. Folate and Vitamin B_{12}	Helps in haemoglobin formation. Development of RBC beyond megaloblastic stage.
		Folate helps in cell division in erythiopoiesis.

IRON DEFICIENCY ANAEMIA

If there is an insufficiency of iron for the formation of haemoglobin, the red blood corpuscles are pale and small and the anaemia is said to be hypochromic and microcytic.

This is the most common form of anaemia throughout the world affecting mainly women in their reproductive years, infants and children. In both rural and urban areas in the tropics, this type of anaemia is extremely common. Iron deficiency is the cause for 1/3 of patients suffering from anaemia.

Aetiology

Deficiency of iron may occur as a result of the following:

Inadequate iron intake: This is secondary to a poor diet such as vegetarian life-style with insufficient haeme iron. The average cereal legume based diets as consumed in most developing countries would appear adequate in iron content (20–22 mg) for an adult. But the availability of iron from such diets is very poor. Only 3–5 per cent of dietary iron is absorbed in normal apparently healthy individual. Ironically good sources of minerals are also good in phytates and the intake of absorption promoters such as meat, fish and ascorbic acid are low in iron.

Infants and children suffer from iron deficiency anaemia due to premature birth, iron deficiency in the mother and prolonged breast-feeding. The elderly often have restricted diets hence may suffer from iron deficiency anaemia.

Inadequate utilisation: This can take place secondary to chronic gastrointestinal disturbances, defective release of iron from iron stores into the plasma and defective iron utilisation owing to a chronic inflammation or other chronic disorder.

Blood losses: It can occur in accidental haemorrhage, in chronic diseases such as tuberculosis, ulcers or intestinal disorders, or excessive blood donation or due to occult (blood or its breakdown products are present in the stool but cannot be seen) blood loss in hookworm infestation. Excessive loss of blood during menstruation and child birth can cause anaemia.

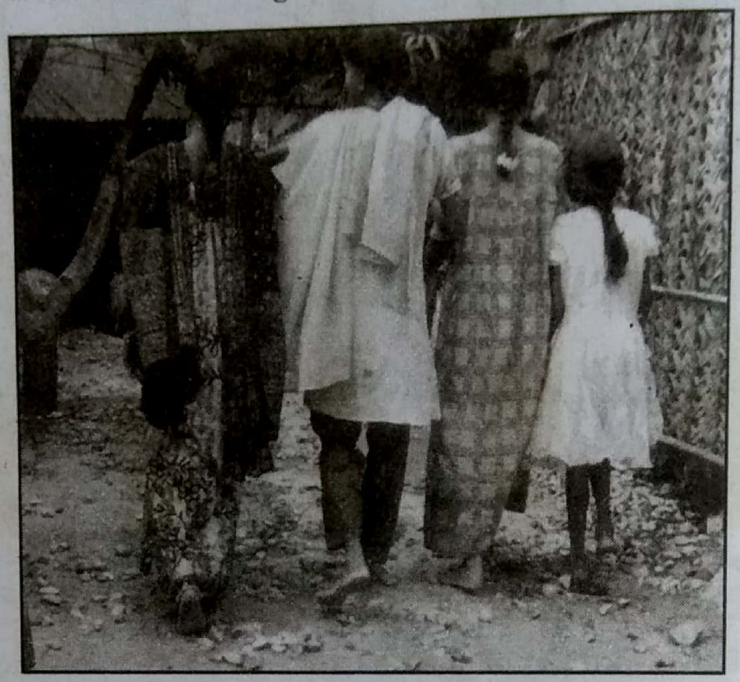


Figure 11g: Walking barefoot can cause hookworm infestation which may ultimately result in anaemia.

In rural areas post partum haemorrhage on account of poor obstetric care leads to iron depletion to a considerable extent. Repeated and closely spaced pregnancies and prolonged periods of lactation deplete iron stores with successive pregnancy and this is reflected in the high incidence of anaemia with higher parity. Resurgence of malaria is another important factor resulting in high incidence of anaemia. In women, using intrauterine contraceptive device, menorrhagia (increased blood loss) may result in further depletion of already poor stores of iron.

Histologic abnormalities of the mucosa of the G.I. tract, such as blunting of the villi are present in advanced iron deficiency anaemia and may cause leakage of blood and decreased absorption of iron, further compounding the problem. Chronic diarrhoea in early childhood be associated with considerable unrecognized blood loss.

Chronic intestinal blood loss can occur by exposure to a heat labile protein in whole cow's milk. Loss of blood in the stools can be prevented either by reducing the quality of whole cow's milk or by using heated or evaporated milk.

Increased demand: Deficiency of iron in the diet during periods of accelerated demand like in infancy (rapidly expanding blood volume), adolescence (rapid growth and onset of menses in girls) and pregnancy and lactation can result in anaemia. Losses of iron may occur due to excessive sweating in tropical climate.

Inadequate absorption: This can occur in diarrhoea (sprue and pellagra) or when there is lack of acid secretion by the stomach or in chronic renal diseases when antacid therapy is given. Gastrectomy impairs iron absorption by decreasing hydrochloric acid and transit time through the duodenum. Excessive amounts of phytates and phosphates in the diet and excess consumption of tea can decrease the absorption of iron.

Decreased iron stores: Pre-term babies, small for dates and twins may have decreased iron stores and susceptible for anaemia.

Diagnosis

Progressive stages of iron deficiency can be evaluated by four different measurements:

1. The plasma ferritin level provides a measure of iron stores.
2. Transferrin saturation can be used as a gauge of iron supply to the tissues. It is calculated by dividing serum iron by Total Iron Binding Capacity. Levels less than 16 per cent are considered to be inadequate for erythropoiesis.
3. Both haemoglobin and hematocrit measurements can indicate anaemia. Most patients develop symptoms of anaemia when the haemoglobin level is approximately 8-11 g/dl.
4. The ratio of zinc protoporphyrin to haeme is a sensitive indicator of iron supply to the developing red blood cells.

When insufficient substrate iron is available to incorporate into porphyrin, zinc is then substituted. Although it can combine with globin and circulate, this zinc-containing molecule cannot bind oxygen.

Anaemia in the newborn is defined as venous haemoglobin less than 13 g/dl in the first two weeks in a term baby and less than 12 g/dl in premature baby. According to National Insititute of Nutrition (2001–02) serum transferrin receptor together with haemoglobin can be used for defining iron deficiency in population surveys.

Table 11.8: Causes of Anaemia in Different Age Groups

Age	Causes
Infancy 0–1 yrs	• Inadequate iron stores at birth due to low birth weight or due to pre-term • Multiple births • Infant who is breast fed by a mother who is a strict vegetarian (vegan) • Infant who is on milk diet without proper weaning foods • Late weaning • Impaired absorption of folate • Regional enteritis, Crohns disease, celiac disease
Childhood 1–9 yrs	• Dietary deficiency • Due to hook worm infestation—occult blood loss • Inflammatory bowel disease • Neglect of female child • Chronic diarrhoea may be associated with considerable unrecognized blood loss.
Adolescence 10–12 yrs	• Menarche • Growth spurt with a suboptimal haematopoitic contents • Gender discrimination • Intensive exercise conditioning as occurs in competitive athletics, iron depletion in girls • Early marriage with pregnancy • Excess blood loss during menstruation

Pregnancy	• Increased requirements • Increased parity • Hemodilution • Low maternal age • Cultural beliefs, taboos and inappropriate food practices • Infections which may interfere with intake, absorption and assimilation of nutrient • Pregnancy related complications
Old age	• Dietary deficiency • Atrophic gastritis • Gastro intestinal blood loss from malignant disease, peptic ulcer • Use of nonsteroidal antiinflammatory drugs • Psychological problems • Poor absorption • Chronic inflammatory disease
Adults	• Chronic infection—tuberculosis, malignancy, chronic diarrhoea, malaria • GI surgery • Histologic abnormalities of the mucosa of the GI tract, such as blunting of the villi ar present in advanced iron deficiency aneamia and may cause leakage of blood an decreased absorption of iron, further compounding the problem. • Infestation with tapeworm, *diphyllobothrium latum* infests the upper intestine.

The peak incidence of iron deficiency in children occurs 6 months to 3 years and 11 years to 17 years.

Table 11.9: Haemoglobin and Haematocrit Cut Offs used to Define Anaemia In People Living at Sea level

Age or sex group	Haemoglobin below g/dl	Haematocrit below %
Children 6 months – 5 years	11.0	33
5–11 years	11.5	34
12–13 years	12.0	36
Non-pregnant women	12.0	36
Pregnant women	11.0	33
Men	13.0	39

Cyanmethaemoglobin (HiCN) is the preferred method for measuring Hb as per recommer International committee of standardisation in haematolory.

Source: WHO/UNICEF/UNV,1998.

Table 11.10: Diagnosis of Iron Deficiency

Indicator	Interpretary guidelines
Peripheral smear	Microcytic hypochromic
MCHC pg*	< 30
Serum Iron µg/dl	< 60
Total Iron Binding capacity µg/dl	> 300
Transferrin saturation %	< 15

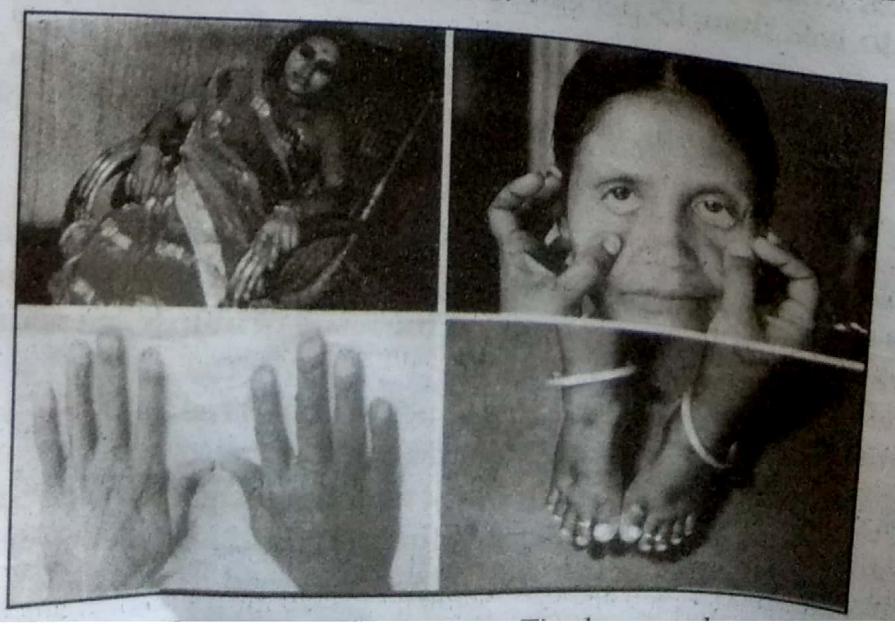
that anaemia due to iron deficiency tends to affect fast acting muscle function (sprint functio whereas cellular deficiency of iron tends to affect endurance exercise.

Figure 11h is given at the end.

Cognitive development: In man, the iron content in the brain increases continuous during the development of the brain and through the teenage period. About 10 per cent of brai iron is present at birth; at the age of 10 the brain has only reached half its normal iron conten and optimal amounts are first reached at the age of 20–30 years. Early iron deficiency may lead to irreparable damage. Iron deficient young adolescents have been shown to score relatively lower in tests of academic performance. Iron deficiency without significant anaemia affects attention span, alertness and learning in infants and children. Depression and disturbances of sleep rhythm also occur in this condition.

Behavioural implications: Anaemic children have been found to be more disruptive, irritable and restless in the classroom. Such changes may be related to functional changes in iron enzymes at cellular level. Iron deficiency is also sometimes associated with pica especially pagophagia (ice eating). Temper tantrum and breath holding spells are also observed in anaemic children. When the haemoglobin level falls below 5 g/dl irritability and anorexia are prominent.

Structure and function of skin and epithelial tissues: Premature loss of hair, alopecia, greying of hair, folliculitis, acne and reduced growth of nails have been reported with iron deficiency with or without anaemia. Mostly tongue, nails, mouth and stomach are affected. The skin may appear pale and the inside of the lower eyelid may be light pink instead of red. Finger nails can become thin and flat and eventually koilonychia (spoon shaped nails) develops. Mouth changes include atrophy of the lingual papillae, burning redness as in severe cases a completely smooth waxy and glistening appearance to the tongue (glossitis). Angular stomatitis and dysphagia may occur. Gastritis occurs frequently and may result in achloryhydria. Progressive, untreated anaemia results in cardiovascular and respiratory changes that can eventually lead to cardiac failure.



glycolytic and citric acid cycle enzymes, specific and nonspecific immune function by involving T cell activation, mitosis, macrophage production and neutrophil myeloperoxidase activity in microbial killing. These functions are so pervasive and so basic for survival that iron deficiency is likely to interfere with function of every organ system in the body.

Treatment

Once anaemia is developed, dietary modification cannot correct the anaemia; supplementation is required. Treatment should focus primarily on the underlying disease or situation leading to the anaemia. Oral administration of inorganic iron in the ferrous form—ferrous sulphate 50–200 mg (60 mg elemental iron) 3 times daily for adults and 6 mg/kg for children. Other salts absorbed at about same degree are ferrous forms of lactate, fumarate, glycine, sulphate, glutamate and gluconate. Carbohydrate iron complexes were initially used only by parenteral route, but recent studies have shown that the therapeutic efficacy and absorption of these compounds are comparable to those of iron salts with lack of adverse effects. Human beings have gutmucosal turnover between 5 and 6 days and absorption is better if iron is administered to new gut cells.

Table 11.11: Response to Iron Therapy in Iron Deficiency Anaemia

Time after iron administration	Response
* 12–24 hrs	Replacement of intracellular iron enzymes; subjective improvement, decreased irritability, increased appetite.
* 36–48 hrs	Initial bone marrow response, erythroid hyperplasia
* 48–75 hrs	Reticulocytosis, peaking at 5–7 days
* 4–30 days	Increase in haemoglobin level
* 1–3 months	Repletion of stores.

Source: Behrman R.E., *et al.*, 2000, Nelson Textbook of Pediatrics, Asia PTE Ltd., Singapore–238884.

Iron is best absorbed when the stomach is empty. However, under these conditions, it tends to cause gastric irritation. Gastrointestinal side effects of nausea, epigastric discomfort and distention, heart burn, diarrhoea or constipation can be minimised by increasing the dose slowly over a few days until the required dosage is reached and by giving the iron in divided doses atleast three times per day. Use of chelated form of iron (bound to amino acids) can result improved absorption and can reduce the likelihood of gastrointestinal distress. Ascorbic acid greatly increases iron absorption through its capacity to maintain iron in the reduced state.

Iron therapy should be continued for several months even after restoration of normal haemoglobin levels, to allow for repletion of body iron stores.

Some behavioural symptoms of iron deficiency seem to respond to iron therapy before the anaemia is cured, suggesting they may be the result of tissue depletion of iron-containing enzymes rather than of a decreased level of haemoglobin.

In iron deficiency anaemia when dietary folate is also low, treatment with iron alone preciptates folate deficiency because more is needed for production of erythrocytes and the supply of folate becomes insufficient.

An improvement in riboflavin status may stimulate iron absorption and turnover to effect an increase in iron store and help in the release of iron from ferritin. In severe iron deficiency sometimes blood transfusion may be necessary. **(Figure 11j is given at the end).**

Prevention

Policies for combating micronutrient malnutrition must be firmly rooted in food based rather than drug based approaches.

Dietary improvement: Proper diet can definitely prevent anaemia.

- The absorption of haeme iron which is derived from meat and flesh foods is better while that of nonhaeme iron derived from cereals, pulses vegetables and fruits is low. Liver is an excellent source of iron. The absorption of nonhaeme iron could however be enhanced by increasing the vitamin C content of the diet. The consumption of tea or coffee along with meals greatly reduces the absorption of nonhaeme iron.
- Regular consumption of iron rich foods (whole grain cereals and pulses, whole grains, nuts, dates, jaggery and foods of animal origin) and vitamin C rich foods (amla, all citrus fruits, guava, green leafy vegetables and salads and seasonal fruits) by all, with special emphasis during pregnancy, lactation, infancy, childhood and adolescence.
- Consuming sprouted pulses regularly after giving some heat treatment as sprouting increases bio-availability of iron as well as increases the content of vitamin C and B-Complex vitamins in the grains and heating destroys the inhibiting factors.
- Incorporating green leafy vegetables (cauliflower greens and arakeerai), seasonal vegetables and fruits in the diet of infants and pre-school children once or twice daily.

Supplementation: Under Reproductive and Child Health Programme (1997) young children and adolescent girls are given iron and folic acid.

Children 6–24 months old are at the greatest risk of the irreversible long-term consequences of iron deficiency namely impaired physical and mental development. They are given 20 mg elemental iron and 100 µg of folic acid in syrup form. Children below 5 years are given 20 mg of elemental iron and 100 µg of folic acid for 100 days in a year.

Adolescent girls on attaining menarche should consume weekly dosage of one IFA tablet containing 100 mg elemental iron and 500 µg of folic acid.

All pregnant mothers are given 60 mg of elemental iron and 500 µg of folic acid for 100 days after the first trimester of pregnancy. Low birth weight infants need iron supplementation from the age of 2 months.

Fortification: Salt fortification with iron has been considered as one of the practical approaches for the prevention and control of iron deficiency anaemia.

Salt is considered as an eminently suitable vehicle for iron fortification in India as it satisfies all the criteria for an ideal vehicle. Salt is consumed in India by all segments of population, rich as well as poor perhaps more by the poor. Salt consumption lies within a narrow range of 12-20 g/day with an average intake of 15 g/day/person. Salt is fortified with ferrous sulphate and one gets 1 mg of iron per gram of fortified salt.

Fortification with iron has been successfully tried for wheat flour, rice, sugar, milk, fish sauce and curry powder. Fortified wheat (iron–12 mg, folic acid 300 µg/200 g) is available in the market. NIN studies (2008-09) indicate that rice fortified with iron, ultra rice, improves iron stores, reduces the morbidities among school children participating in the mid-day meal programme. Fortification of rice with iron, ultra rice, through mid day meal programme can be considered as a strategy to prevent iron deficiency among children.

BIONUTRITION

A high yielding iron rich rice, has been developed by Philippine researchers at Manila. This variety has been designed to tolerate low temperatures and is rich in iron and zinc. It has good flavour, texture and cooking qualities. No biotechnology is involved.

Education

Nutrition education related to iron and anaemia should be given to the community.

- Promotion of consumption of pulses, green leafy vegetables, other vegetables (whi are rich in iron and folic acid) and meat products rich in bio-available iron, particular by pregnant and lactating mothers.
- Creation of awareness in mothers attending antenatal clinics, immunisation sessio anganwadi centres and creches about the prevalence of anaemia, ill effects of anaem and its preventable nature.
- Addition of iron rich foods to the weaning foods of infants.
- Regular consumption of foods rich in vitamin C such as oranges, guava, amla etc. ne to be encouraged to promote iron absorption.
- Promotion of home gardening to increase the availability of common iron rich foo such as green leafy vegetables.
- Discouraging the consumption of foods and beverages like tea and tamarind th inhibit iron absorption especially by the vulnerable groups like pregnant women a children.
- Control of parasitic worms and malaria.

Anaemia can be prevented by food based strategies and by supplementation, fortificati and education.

QUESTIONS

1. Write the importance of following:
   (*a*) transferrin (*b*) ferritin (*c*) haeme iron
2. Discuss the factors that affect iron absorption.
3. Explain clinical findings of iron deficiency anaemia.
4. What is haemochromatosis? How is it different from siderosis?
5. Give the RDA of iron for different age groups.
6. Name three haeme iron sources and three nonhaeme iron sources.
7. Explain the cycle of haemoglobin.
8. The body recycles iron. Inspite of that, iron deficiency anaemia occurs. Why?
9. What is the role of hydrochloric acid in the absorption of iron?
10. Give the causes of anaemia in pre-school children.
11. Define anaemia.
12. What measures are taken to prevent anaemia in India?
13. Explain prevalence of anaemia in India.
14. Explain the criterion used to diagnose iron deficiency anaemia.

10.6 SELENIUM

The element selenium was discovered in 1817 in association with the element sulphur. However, selenium as an essential nutrient remained unrecognized for many years, although selenium toxicity in horses and cattle, "blind staggers" and "alkali disease" was known since the 1930s.

The first description of the dietary selenium deficiency in isolated populations in the People's Republic of China, was made in 1979. The disease known as *Keshan* disease, named for the country where it was first recognized, was characterized by cardiomyopathy affecting primarily children and young women. The disease was often fatal. The second selenium deficiency disease Kashin-Beck disease was reported in 1980. It was prevalent in China and Sino-Soviet border. Both the diseases were caused primarily due to selenium deficiency in the soil.

Selenium is a non metallic element and exists in several oxidation states which include Se^{2+}, Se^{4+} and Se^{6+}. The chemistry of selenium is similar to that of sulphur. Selenium replaces sulphur to form organic compounds such as selenocysteine and selenomethionine. Total selenium content of the body varies from 3-15 mg depending on the dietary intake. Approximately 30% of tissue selenium is contained in the liver, 15% in kidney, 30% in muscle and 10% in blood plasma. Much of tissue selenium is found in proteins as selenoanalogues of sulphur amino acids; other metabolically active forms include selenotrisulphides and other acid-labile selenium compounds.

In the body, selenium can be bound to selenium-binding proteins. It can also be directly incorporated into selenoprotein during translation at the ribosome complex using a RNA specific for the amino acid–selenocysteine. Thus selenocysteine can be considered as the 21" amino acid in terms of ribosome-mediated protein synthesis. At least 15 selenoproteins have now been characterized. Table 10.12 provides a list of these selenoproteins. We will learn about them later in the function section.

Table 10.12: A selection of characterized selenoproteins

Protein	Tissue Distribution
Cytosolic GSHPx	All, including thyroid
Phospholipid hydroxide GSHPx	All, including thyroid
Gastrointestinal GSHPx	Gastrointestinal tract
Extracellular GSHPx	Plasma, thyroid
Thioredoxin reductase	All, including thyroid
Iodothyronine-delodinase (type 1)	Liver, kidneys, and thyroid
Iodothyronine-deiodinase (type 2)	Central nervous system and pituitary
Iodothyronine-deiodinase (type 3)	Brown adipose tissue, central nervous system, and placenta
Selenoprotein P	Plasma
Selenoprotein W	Muscle
Sperm capsule selenoprotein	Sperm tail

* GSHPx, glutathione peroxidase.

Next, we shall brief ourselves regarding the presence of selenium in food.

Food Sources

Environmental conditions and agricultural practices have a profound influence on the selenium content of many foods. Table 10.13(a) illustrates the wide range of selenium content of the principal food groups and the variability in the selenium content of dietary constituents in selected counties. This variability is exceeded only by that found in the iodine content of foods.

Table 10.13: The selenium contents of foods and diets

a) *Typical ranges of selenium concentrations (ng/g fresh weight) in food, groups*

Food Group	India	United States	International Compilation
Cereals and cereal products	5-95	10-370	10-550
Meat, meat products, and eggs	40-120	100-810	10-360
Fish and marine	280-1080	400-1500	110-970
Fish and freshwater	–	–	180-680
Pulses	10-138	–	–
Dairy products	5-15	10-130	1-170
Fruits and vegetables	1-7	1-60	1-20

b) *Typical distribution of selenium in dietary constituents (µg/day) in selected countries*

Food Groups	China		India		Finland	United Kingdom
	Keshan Disease Area	Disease Free Areas	Low-income Vegetarian Diets	Low-income Conventional Diets		
Total diet	7.7	16.4	27.4	52.5	30.0	31.0
Cereals and cereal products	5.4	11.6	15.7	21.1	2.8	7.0
Pulses	–	–	3.9	3.6	1.1	–
Meat and eggs			–	3.7	9.2	10.0
Fish	0.6	2.2	–	18.4	9.5	4.0
Dairy products			6.9	4.8	6.5	3.0
Fruits and vegetables	1.7	2.6	0.9	0.9	0.5	6.0
other	–	–	–	–	1.1	3.0

Source: Vitamin and Mineral Requirement in Human Nutrition, FAO/WHO (2004)

Geographic differences in the content and availability of selenium from soils to food crops and animal products have a marked effect on the selenium status of entire communities. Refer to Table 10.13(b) which presents the typical distribution of selenium in dietary constituents in selected countries. As you would notice, the distribution of Keshan disease and Kashin-Beck disease in China reflects the distribution of soils from which selenium is poorly available to rice, maize, wheat and pasture grasses.

Selenium enters the food chain through plants. The concentralion of selenium in plants is directly related Io the concentration of the mineral in the soil on which plants were grown. Among the different trace elements, selenium varies greatly in its soil concentration. It has been suggested that <10 ng/g for grain selenium and <3 ng/g for water-soluble soil selenium could be used as indices to define deficient areas.

The absorption of selenium by plants is not only dependent on the concentration of selenium in the soil but also on pH, microbial activity, rainfall and the chemical form of selenium. Higher plants can absorb selenium as selenate and can synthesize selenomethionine and to a lesser extent, selenocysteine.

Owing to all above factors, the selenium content in food varies greatly. Overall, animal products, especially organ meats, are thought to contain more selenium than plant sources, as you may have noticed in Table 10.13 (a). Seafoods are also considered good sources, although availability of the mineral from fish, especially those containing mercury, is low.

Selenium occurs in foods in organic form, such as, selenomethionine, selenocysteine, selenocystine and Se-methyl selenomethionine. In general, plant foods contain greater proportion of organic selenium compounds. Inorganic forms include selenite (H_2SeO_3) and Selenate (H_2SeO_4). These forms are found in some vegetables.

Next, we shall discuss about the absorption, transport, storage and excretion of selenium.

Metabolism

Selenium compounds'are generally very efficiently absorbed by humans and selenium absorption does not appear to be' under homeostatic control. selenium is mainly absorbed from the duodenum. Less absorption occurs in the jejunum and ileum. Inorganic forms of selenium (mainly selenate) are passively transported whereas organic forms are actively transported.

Almost 50-80% of dietary selenium is absorbed, with efficiency being higher for organic forms, as compared to inorganic. Among the organic forms, selenomethionine is better absorbed than selenocysteine. Among the inorganic forms, selenates are better absorbed than selenites. For example, absorption of the selenite form of selenium is greater than 80% whereas that of selenium as selenomethionine or as selenate may be greater than 90%. In addition, some dietary factors appear to influence the absorption of the element. Phytates and heavy metals, such as mercury through chelation and precipitation, hinder selenium absorption. Vitamins C, A and E, as well as, glutathione enhance the absorption.

Refer to Figure 10.5 for a better understanding of selenium absorption.

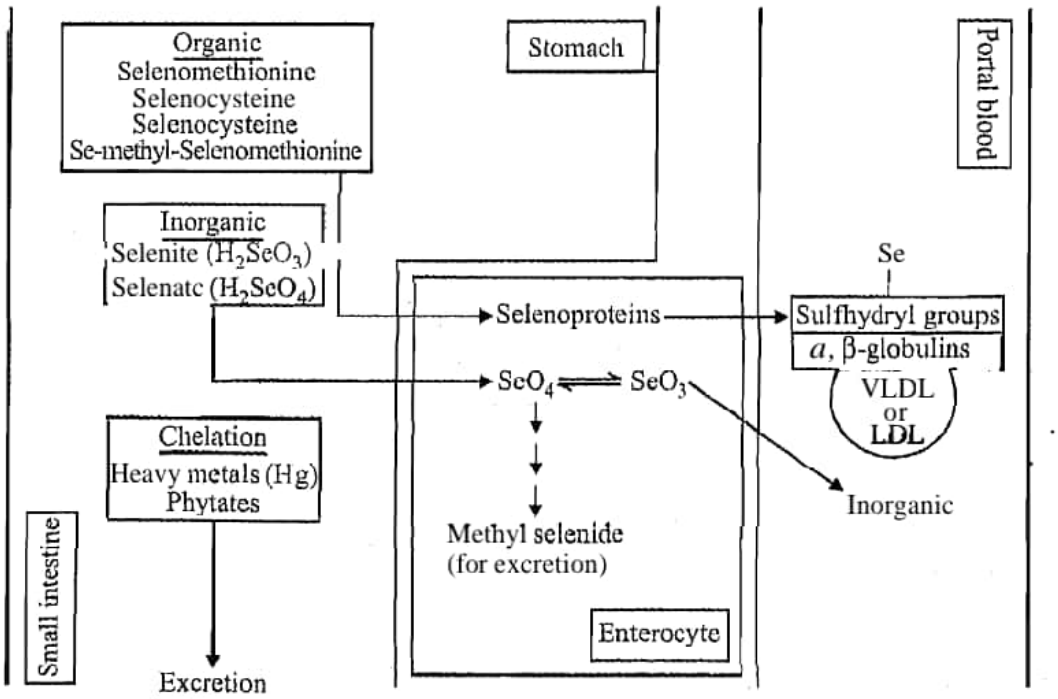


Figure 10.5: Absorption and transport of selenium

As you may have noticed in Figure 10.5, after absorption selenium binds to sulphydryl groups in a and β globulins of VLDL and LDL to be transported to the different tissues. Liver and kidneys appear to be the major target organs.

Within tissues such as liver, organic, as well as, inorganic selenium compounds have different fates. This is briefly discussed herewith:

1) Selenomethionine obtained from the diet may be:

- stored as such in amino acid pool,
- used for protein synthesis, and
- catabolized to selenocysteine.

2) Selenocysteine obtained from the diet or after catabolism of selenomethionine is degraded to yield free elemental selenium. This elemental selenium may be:

- attached to tRNA charged with serine to be incorporated in selenium dependent enzymes, and
- converted into selenite which may be stored or excreted,

3) Selenate from the diet is converted to selenite. Selenite is further converted to selenide. Selenide may be:

- converted to selenophosphate to yield free selenium, which is incorporated into enzymes, and
- excreted as methyl selenide.

The above discussion can be clearly understood after going through Figure 10.6, which illustrates the metabolic fate of.selenium.

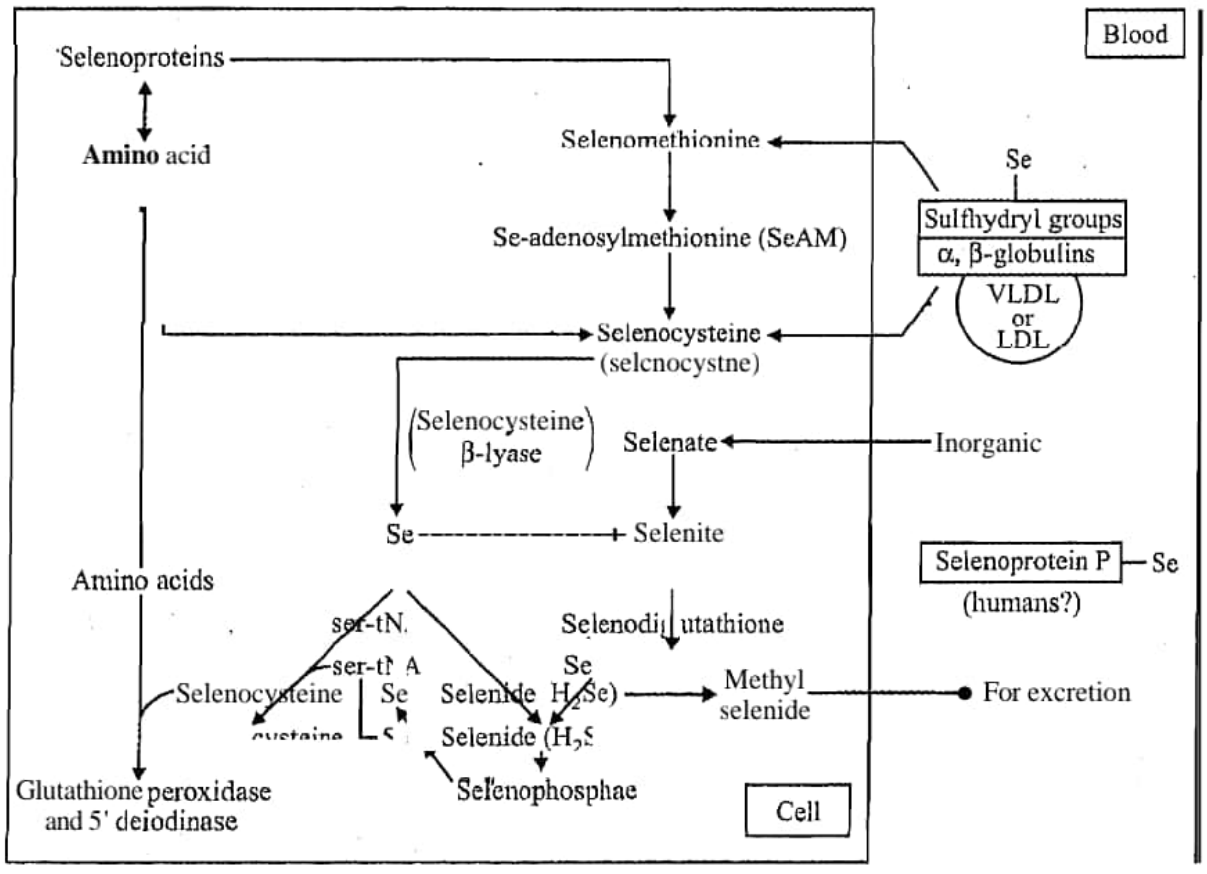


Figure 10.6: Metabolism of selenium in tissues

4) Selenium is excreted from the body almost equally in the urine (as methyl selenium) and faeces (unabsorbed selenium, biliary, pancreatic and intestinal secretion). Unlike copper, selenium is rapidly excreted in urine. Selenium losses through lungs and skin also contribute to daily selenium excretion.

After having read about the presence of selenium in human body and its association with several disease conditions, it must be evident that selenium plays an important

role in maintaining our health. The most salient functions of selenium have been discussed next.

Functions

Until recently, the only known metabolic role of selenium in humans was as a component of glutathione peroxidase which along with vitamin E and superoxide dismutase forms a part of the anti-oxidant defense system. However, more selenoproteins are being discovered and currently it is estimated that 50-100 selenoproteins are present in animals. Selenoproteins in animals and humans are involved in protection from oxidative damage, maintaining adequate thyroid hormone status and protection from injury by a heavy metal like mercury.

Three major enzyme systems in which selenium plays an important role have been identified in humans. These include:

a) Glutathione peroxidases,

b) Iodothyronine deiodonases, and

c) Selenoproteins P and W

Let us study them in greater detail.

a) *Glutathione peroxidases:* The role of selenium in the cytosolic enzyme, glutathione peroxidase (GSHPx), was first illustrated in 1973. Four selenium dependent glutathione peroxidases have been identified and named as Glutathione peroxidases 1-4 ($GSHP_{xs}$ 1-4). During stress, infection, or tissue injury, selenoenzymes may protect against the damaging effects of hydrogen peroxide or oxygen-rich free radicals. This family of enzymes catalyzes the destruction of hydrogen peroxide or lipid hydroperoxides according to the following general reactions:

$$H_2O_2 + 2GSH \longrightarrow 2H_2O + GSSG$$

$$ROOH + 2GSH \longrightarrow ROH + H_2O + GSSG$$

where, GSH is glutathione and GSSG is its oxidized form.

Thus, from the reaction above, it is evident that the main role of glutathione peroxidases is to reduce hydrogen .peroxide and free hydroperoxides in different cells and tissues by using glutathione (GSH) as the hydrogen donor. Thus, the reactive species of hydroperoxide free radicals are converted into innocuous molecules of water. $GSHP_{x-1}$ is present in virtually all cells, $GSHP_{x-2}$ is localized in the gastrointestinal tract, $GSHP_{x-3}$ is present in plasma while $GSHP_{x-4}$ is most abundant in testis but present in other tissues also.

$GSHP_{x-4}$ plays a major role in protecting against lipid peroxidation as it is the only intracellular enzyme that can reduce fatty acid hydro peroxide, $GSHP_{x-3}$ in plasma can also perform this role.

b) *Iodothyronine Deiodinases:* Another group of selenoproteins are the iodothyronine deiodinases essential for the conversion of thyroxine or tetraiodothyronine (T_4) to its physiologically active form tri-iodothyronine (T_3). Three types of iodothyronine deiodinases have been identified, all of them being selenoproteins. When one iodine is removed from T_4, it is converted T_3. T_3 is more active than T_4. Thus, one of the deiodinase enzymes is involved in activating T_4. When one or more iodine is removed from T_3, the resulting molecules do not have enzyme activity. Therefore, another selenium-dependent deiodinase inactivates T

Type I iodothyronine deiodinase (a selenoprotein) is found in liver, kidney and thyroid tissue. The major role of this enzyme is to provide T_3 to peripheral tissues by deiodinating T_4 secreted by the thyroid gland. Selenium deficiency causes a decline in the Type I deiodinase enzyme activity, but it may not result in hypothyroidism as there is a compensatory increase in plasma T_4 levels. *Type II iodothyronine deiodinase*, also a selenoprotein, is present in the brain, pituitary and placenta. The major function of this enzyme is to regulate T_3 levels in these tissues, and control the secretion of thyroid stimulating hormone. Type II enzyme activity is also reduced in selenium deficiency. *Type III iodothyronine deiodinase*, another selenoprotein, is involved mainly in degradation of the T_4 and T_3. How this enzyme is affected in selenium deficiency is not fully investigated.

Thus, these selenoprotein enzymes regulate and maintain thyroid levels. Animal studies have shown that a combined deficiency of selenium and iodine produces much more severe hypothyroidism compared to iodine deficiency alone. Further, maternal deficiency of selenium and iodine is implicated in cretinism in newborn – the most severe outcome of thyroid hormone deficiency during pregnancy.

c) *Selenoproteins P and W*: The third group comprises of *selenoprotein P*, an extracellular constituent with multiple selenocysteine molecules. This has an antioxidant role, deactivating free radicals. *Selenoprotein* W, present in the muscle has a suggested role in muscular degeneration seen in combined selenium and vitamin E deficiency. Selenoprotein W gets reduced during selenium deficiency.

Another group of selenium-containing enzymes is the *thioredoxin reductases.* The selenoenzyme thioredoxin reductase is involved in disposal of the products of oxidative metabolism. It contains two selenocysteine groups per molecule and is a major component of a *redox system* with a multiplicity of functions, among which is the capacity to degrade locally excessive and potentially toxic concentrations of peroxide and hydroperoxides likely to induce cell death and tissue atrophy.

These selenoproteins catalyze the NADPH–dependent reduction of oxidized thioredoxin. Reduced thioredoxin provides reducing equivalents for various redox-dependent systems, such as, ribonucleotide reductase essential for DNA synthesis, redox regulation of transcription factors. Besides, these proteins have important functions in regulating cell growth and inhibiting apoptosis.

The above discussion clearly indicates the importance of selenium in human nutrition. Let us now find out how selenium status can have an impact on our health. We shall ,begin with the state of deficiency and then discuss the consequences of toxic levels of selenium.

Deficiency

Selenium deficiency has been linked to two regional human diseases: *Keshan disease* and *Kashin Beck's disease.*

Let us understand what these diseases are and their characteristic features.

Keshan disease: It is a cardiomyopathy (disease of the myocardium, involving heart muscle) that was identified to affect children and women of child bearing age in China. Sudden onset of insufficient heart function is characteristic of the acute form of this disease while in chronic Keshan disease, heart enlargement and insufficiency exist. Intervention trials comprising more than a million subjects in China has demonstrated the protective effect of selenium against Keshan's disease. It is important to note that selenium supplements cannot however reverse cardiac failure if it has occurred.

Kashin Beck disease: Kashin Beck disease was identified to affect growing children in parts of Siberian Russia and China. It is characterized by osteoarthritis involving degeneration and necrosis of the joints and epiphyseal-plate cartilages of legs and arms. It is possible that apart from selenium deficiency, many other factors may be contributing to the development of Kashin Beck's disease.

Suboptimal selenium status may be widespread in human population. It is accompanied by loss of immuno-competence with the impairment of both cell-mediated immunity and β-cell function. The early preclinical stages of development of human immunodeficiency virus (HIV) infection are accompanied by a very marked decline in plasma selenium. Subclinical malnutrition assumes increased significance during the development of acquired immune deficiency syndrome (AIDS). Selenium supplementation in subjects has been shown to mark irnmuno-stimulant effects including increased proliferation of activated T-cells. In addition, as selenium has well recognized anti-oxidant and anti-inflammatory roles, other oxidative stress or inflammatory conditions such as rheumatoid arthritis, ulcerative colitis, pancreatitis may also benefit from selenium supplementation.

Further, enhancement of the virulence of virus due to selenium deficiency has been reported. There is a growing evidence that suboptimal selenium status may also increase risk of cancer and cardiovascular disease. However, much work is still needed in these aspects.

Toxicity

There is a narrow margin between the beneficial and harmful intakes of selenium. The level at which selenosis occurs is not well-defined but threshold for toxicity appears to be 850-900 μg per day. Symptoms of chronic toxicity include brittle hair and nails, skin lesions with secondary infections and garlic odour in the breath. Chronic selenium poisoning in people is characterized primarily by loss of hair and changes in finger nail morphology. In some cases, skin lesions may occur.

Next, we shall learn about the parameters indicative of selenium status.

Assessment of Selenium Status

Blood glutathione (GSH) peroxidase activity is directly related to blood selenium up to a level of 1.27 μmoles/L. Beyond this point, the activity of the enzyme plateaus and therefore cannot be used for assessing selenium status. As of now, GSH peroxidase remains a useful index over the assessment of usual dietary intakes but is limited by the peak level reached at 1.27 mmol/L. Plasma selenium level is an index of short term status, as it has been shown to respond to selenium supplementation more rapidly in deficient individuals than whole blood selenium. Hair and nail selenium are not as yet established as valid parameters, although they are being investigated.

So what level of intake should be maintained to ensure the maintenance of optimum selenium levels in plasma? Let us find out.

Requirements

The FAO/WHO 2004 recommendation for nutrient intake for selenium by groups is given in Table 10.14. How do these recommendations compare with the US and the UK recommendations? Let us find out. In the UK, the reference nutrient intake has been set at 75 and 60 mcg of selenium per day for men and women, respectively. These are based on the intakes required to saturate plasma glutathione peroxidase. In the U.S., recommended nutrient intake is 70 mcg/day for men and 55 mcg/day for women. Thus, the present FAO/WHO 2004 report represent a significant decrease in the suggested need for selenium. The lower requirements presented are physiologically justifiable and will only give rise to concern if there are grounds for serious uncertainty as to the predictability of dietary selenium intake.

Table 10.14: **Recommended nutrient intakes by selenium, by group**

Group	Assumed body Weight (kg)	RNI (ug/kg)[b]
Infants and Children		
0 - 6 months	6	6
7 - 12 months	9	10
1 - 3 years	12	17
4 - 6 years	19	22
7 - 9 years	25	21
Adolescents		
Females 10 - 18 years	49	26
Males 10 - 18 years	51	32
Adults		
Females, 19 - 65 years	55	26
65+ years	54	25
Males, 19 - 65 years	65	34
65+ years	64	33
Pregnant women	–	28
Second trimester	–	30
Third trimester		
Lactating		
0-6 months	–	35
6 - 12 months	–	42

[b] Recommended nutrient intake (RNI) derived from the average $Se_R^{normative}$ + 2 x assumed standard deviation (of 12.5%).

Source: Vitamin and Mineral Requirements in Human Nutrition, FAO/WHO (2004)

No RDI's have been suggested so far for Indians. There is a need to derive recommendations which are applicable for a proportionally lower weight range than that utilized in most developed countries.

Before we proceed to study chromiun, let us recapitulate what we have learnt so far by answering the check your progress exercise 4.

Check Your Progress Exercise 4

1) Name an enzyme which constitutes selenium as its integral part.

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2) Of all trace elements, selenium content in food varies greatly. Why?

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3) What are the factors which hinder selenium absorption?

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.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,

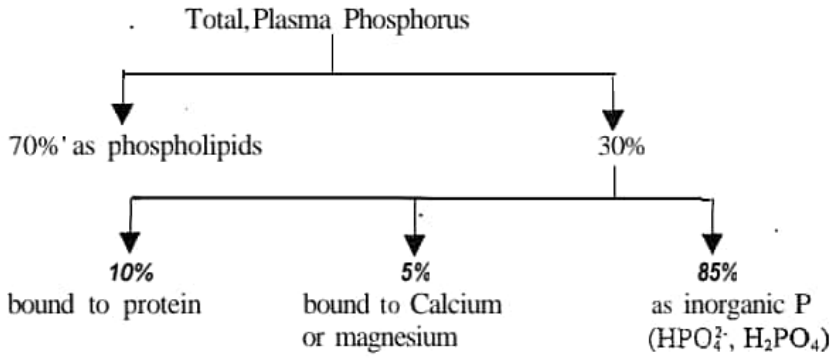

Figure **9.1:** Phosphorous distribution in plasma

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.

.....

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

PHOSPHORUS

Phosphorus constitutes approximately 1 per cent of the weight of the human body, largely in the form of phosphate (PO_4). Upto 90 per cent of phosphorus in the body is found within calcium phosphate (apatite) crystals in bones and teeth.

FUNCTIONS

Mineralisation of Bones and Teeth

Phosphorus in the form of phosphate is an essential part of bone as is calcium. Phosphate is present as part of hydroxy apatite crystals.

Facilitation of Energy Transactions

Energy released during the oxidation of carbohydrates, fats, proteins and alcohol is stored by cells within the structure of the phosphate–containing compound adenosine triphosphate (ATP). The presence of phosphorus in ATP and also adenosine diphosphate (ADP) and various coenzymes involved in energy transaction makes phosphorus essential for the capture and use of energy by all cells.

Absorption and Transport of Nutrients

Many nutrients must be combined with phosphate groups before they are able to be transported across cell membranes and hence absorbed into the body and distributed among its various cells and tissues. Thus the phosphorylation of nutrients and other biochemicals is essential for their proper distribution within the body.

Regulation of Protein Activity

Many proteins including many enzymes are turned 'on' or 'off' by phosphorylation reactions that attach phosphate groups to particular amino acids within the proteins concerned. These

phosphorylation reactions are involved in controlling the activities of proteins that in turn control the rate of cell growth and cell division and the extent to which the specific genes within cell nuclei are active.

Component of Essential Body Compounds

ATP, ADP and various co-enzymes and regulated proteins require phosphorus as part of their chemical structure. Many other vital compounds like DNA of genes, RNA that carries the genetic message from the nucleus to the cytoplasm, the phospholipids of cell membranes and some vitamins contain phosphorus as a necessary part of their structure.

Regulation of Acid-Base Balance

Phosphate ions, hydrogen phosphate ions and dihydrogen phosphate ions are the major anions in blood plasma. These ions maintain acid base balance by combining with excess hydrogen ions when condition becomes too acidic and yet release hydrogen ions when conditions threatens to become too alkaline. The phosphate ions and phosphate containing compounds act as buffers against excessive variation in the pH level of fluids in the body.

ABSORPTION AND METABOLISM

Phosphorus can be released from phosphorus-containing compounds in food by the action of intestinal enzymes known as phosphatases and is then absorbed into the blood plasma with the help of vitamin D. The level of phosphorus in the blood is regulated by parathyroid gland, which interacts with vitamin D to control the amount of phosphorus absorbed, the amount retained by the kidneys and the amount either released from or deposited in bone.

In healthy people the rate at which phosphorus is absorbed from the gastrointestinal tract and excreted via the kidneys are equal, maintaining total body phosphorus at a steady level. Approximately 90 per cent of ingested phosphorus is excreted via the kidneys, with the remaining 10 per cent lost directly from the gastrointestinal tract without being absorbed. If plasma phosphorus levels decline, reabsorption of phosphorus by the kidneys increases to compensate and if plasma phosphorus levels rise too high, no phosphorus is reabsorbed in the kidneys.

If plasma phosphorus levels fall below 2.5 mg/100 ml hypophosphatemia results. This can result from either inadequate absorption of phosphorus from the gastrointestinal tract or increased excretion of phosphorus via the kidneys. Loss of phosphours occurs in diarrhoea, by use of laxatives and when there is loss of intestinal tissue for any reason. Conditions that increase phosphorus excretion are generally those that lead to increased secretion of parathyroid hormone such as hyperthyroidism, certain forms of kidney disease and certain cancers.

DEFICIENCY

As phosphorus is widely distributed in foods, deficiency is hardly found in humans. However, people who consume large amount of antacids (interfere with absorption) people who suffer

excessive losses in urine (dialysis) and prematurely born infants may suffer from deficiency of phosphorus. Vitamin D deficiency and prolonged parenteral nutrition can cause phosphorus deficiency.

Deficiency of phosphate may produce osteomalacia, myopathy, growth failure and defects in leucocyte function.

RECOMMENDED DIETARY ALLOWANCES

The RDA for phosphorus for children and adults corresponds to an intake that is at least equal to the calcium allowance during the growth period but no more than twice that amount. During infancy the Ca : P ratio suggested is 1 : 1.5.

Table 10.5: ICMR Recommended Dietary Allowance of Calcium and Phosphorus mg/day - 2010

Group	Calcium	Phosphorus
Man	600	600
Woman	600	600
Pregnancy and lactation	1200	1200
Post menopausal women	800	600–800
Infants	500	750
Children		
1–9 years	600	600
10–15 years	800	800
16–18 years	800	800

CALCIUM: PHOSPHORUS RATIO

The ratio of plasma Ca : P is important for calcification of bones. The product of Ca×P (in mg/d) in children is around 50 and in adults around 40. This product is less than 30 in rickets.

During rapid growth and calcification the diet should have a calcium: phosphorus ratio 1 : 1. When calcium is required only for maintenance as in adults, the calcium requirement is lower both absolutely and relatively to the phosphorus requirement. Thus the Ca : P ratio is highest at the earliest age: (1 : 1), decreases with the attainment of adult status (1 : 2) and then in the case of the female increases again (1 : 1) in the latter part of pregnancy and during lactation. In the normal adult man the calcium: phosphorus ratio of the whole body is a little under 1 : 1 and that of the bone is a little over 2 : 1.

SOURCES

Practically all foods contain significant amounts of phosphorus, although it is particularly abundant in protein rich foods. Meat, fish, poultry, eggs, dairy products and cereal products like rice are the primary sources of phosphorus in an average diet.

Table 10.6: Phosphorus Content of Foods

Food	Phosphorus mg/100g
Rice bran	1410
Skim milk powder	1000
Soyabean	690
Carrot	530
Cheese	520
Almonds	490
Rajamah	410
Walnut	380
Liver sheep	380
Mackerel	305