

Iron

What is the major form of dietary iron?

Ingested iron is in 2 main forms:

- Iron bound in haem (eg from myoglobin and red cells in red meats)
- Iron bound to organic ligands in other food (most of this is in the ferric form.)

Some foods have high levels of iron but contain other substances which bind to the iron and prevent its absorption (eg oxalate in spinach). This does not affect absorption of iron bound in haem.

Can you tell me about the absorption of iron?

Iron is absorbed by the enterocytes in the duodenum and upper jejunum by several pathways in the apical membrane of the enterocytes.

Firstly: Consider absorption of iron in the ferrous and ferric forms (eg iron salts)

Dietary Fe^{+3} (ferric) form is converted to the Fe^{+2} (ferrous) form in the stomach. This reduction is greatly promoted by the presence of H^+ and dietary ascorbic acid. The great advantage of this conversion is that the ferrous form (as compared to the ferric form) is much more easily released from the organic ligands to which it is bound and stays soluble. Ferric iron precipitates at $\text{pH} > 3$ (as found in the duodenum) and is not available for absorption from such precipitates. Ferrous iron remains soluble up to pH values of about 7.5 and is available for absorption. (Duodenal pH increases from 4 to about 7)

In addition at the low gastric pH, some substances (eg some amino acids) can bind with ferric iron to form a soluble chelate from which iron can be absorbed in the duodenum. (Other substances such as phytates and tannates form insoluble precipitates and prevent iron absorption).

So the ideal situation is either:

- Reduction of ferric iron (to ferrous iron) which can remain soluble at physiological pH in the duodenum, *or*:
- The formation of soluble chelates from which ferric iron can be readily released at the apical membrane of the duodenal enterocyte.

Both these processes are facilitated by a low gastric pH.

The absorption pathway in the apical membrane of the enterocyte involves both a ferrireductase and a membrane transport protein (known as divalent metal transporter 1 or DMT1). The ferrireductase converts any free ferric iron into the ferrous form. The ferrous form is then transported across the membrane by DMT1. The gene for DMT1 contains an iron regulatory element and is consequently subject to control. Note that there are no transferrin receptors on this membrane and transferrin is not involved in this absorption. DMT1 also transports several other divalent metal ions.

There is probably another pathway for absorption of ferric iron: the mobilferrin-integrin pathway. This means that ferrous & ferric iron can be absorbed by separate routes.

Secondly: Consider the absorption of haem.

Dietary haemoglobin & myoglobin is degraded releasing haem. Haem is soluble in the alkaline duodenal contents but almost insoluble at a $\text{pH} < 6$. It is readily absorbed as an intact metallo-porphyrin by the mucosal cells by a process involving a haem receptor. This process is independent of the ferrireductase-DMT1 and the mobilferrin-integrin pathways. Haem is broken down in the enterocyte by haem oxygenase releasing the Fe^{+2} .

This absorption of iron bound in haem provides an additional route for the absorption of iron in the small bowel.

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As mentioned previously, iron is absorbed in the proximal small bowel (ie mostly duodenum). Once in the cytoplasm, iron (in the ferric form) can either bind to apoferritin to form ferritin (storage form in the cell) or be transported across the basolateral membrane into the blood.

Ferrous iron is transported across the basolateral membrane by ferroportin (aka Ireg1). This is coupled to a copper-containing ferrioxidase (hephaestin) which converts the iron to the ferric form. This binds to the blood transport protein, transferrin. Each transferrin molecule has two sites where it can bind Fe^{+3} . Under typical conditions of iron balance, the plasma transferrin is about one-third saturated with iron.

How much iron is absorbed per day?

For iron balance, the amount absorbed per day equals the amount lost per day. Typically this is 0.6 to 1 mg/day for an adult male, and 2.1 mg/day for an adult female. Female average requirements are higher because of menstrual loss of blood. This is only 5 to 10% of the iron in a typical Western diet. The amount of iron absorbed increases markedly during pregnancy and in iron deficiency.

How much iron is in the body?

How is this distributed?

Why is iron always present in a bound form?

Total body iron stores in a 70kg male are about 3,500 to 3,700 mgs. An adult female has lower iron levels due to lower weight and lower haemoglobin levels and increased losses. Nearly all iron is bound with protein. Iron is distributed in 3 major pools in the body:

<i>Functional pool</i>		
• Bound in haemoglobin	65 to 70%	2,500mg of iron
• Bound in myoglobin	3 to 5%	130mg
• Bound to other proteins	0.2%	8mg
<i>Transport pool</i>		
• Bound to transferrin:	0.1%	4mg
<i>Storage pool</i>		
• Bound in ferritin (most in liver)	25 to 30%	1,000mg.

Iron is a very chemically active and potentially toxic substance. It binds nonspecifically to many proteins and impairs their function, and it acts as a catalyst in many oxidation reactions (eg lipid peroxidation in the cell membrane). To avoid these damaging reactions, iron in the body is *always* present in a bound form with proteins. Consequences of this are:

- There is no physiological control mechanism for excretion of iron from the body.
- Control of the body's iron content is *solely* by regulation of absorption.

Iron is lost from the body with menses in females, and other blood losses (eg minor skin wounds) and with cell sloughing but:

- the amount of iron involved is generally small, and
- these processes are uncontrolled.

What is meant by the term 'mucosal block' as applied to iron absorption?

What is the function of this block? What happens in the situation of iron deficiency?

Control of iron stores in the body occurs at the level of the small bowel mucosal cells (enterocytes). This mucosal control of iron absorption has been called a *mucosal block* (or *mucosal intelligence*) as it prevents excessive amounts of iron entering the body. The full details of the control of iron absorption are not fully determined.

In conditions where the mucosal control mechanism malfunctions (eg haemochromatosis), this will cause iron overload. The body cannot excrete the excessive amount absorbed in this condition and the excess iron precipitates in the tissues causing damage.

If iron stores in the body are low, the plasma level of transferrin is high, its iron saturation is low and more iron passes from ferritin in the mucosal cells to transferrin in the blood.

If iron stores are adequate, saturation of transferrin is higher and the iron remains in the enterocyte. Enterocytes turn over frequently and the iron is lost when the cell is shed. Iron is readily absorbed into the enterocyte but the net amount absorbed from the enterocyte across its basal membrane is controlled by ferritin and transferrin levels and saturation. Unwanted iron is lost when the enterocytes are shed.

Overall, this mucosal control process works well. Net iron absorption is typically only about 5 to 10% of dietary iron. The mucosal block is a relative one: it can be overwhelmed if dietary iron is high (eg high dietary intake of some iron salts as in iron tablets).

What is the absorbed iron used for?

How does iron enter cells?

The major functional use of iron in the body is in haem bound to proteins. Quantitatively, haemoglobin is the most important protein involved. Other haemoproteins are myoglobin, cytochromes, catalase and most oxidases. All haemoproteins are involved with oxygen or involve oxidation processes.

About 20 to 25 mg of iron is used in haemoglobin synthesis each day. This is far more than the net amount of iron absorbed (say 1 to 2 mg/day) because the body recycles the iron liberated from red cell breakdown. This iron is carried to the bone marrow on transferrin.

All cells require iron (eg cytochromes for oxidative phosphorylation in all cells with mitochondria). Red cells do not contain mitochondria but have iron in haem. Transferrin transports iron to the cell membrane. It binds to specific transferrin receptors and is internalised by *endocytosis*. The iron is released and the transferrin molecule is then returned intact to the interstitial fluid. Many tissues can store iron in ferritin.

Tell me about ferritin and apoferritin?

Ferritin is the major storage form of iron in the body. The enterocytes and liver (& indeed many other body cells) produce a protein called apoferritin which binds iron and this complex of apoferritin and iron is known as ferritin.

Apoferritin consists of 24 polypeptide subunits composed of L (light) and H (heavy) chains. These subunits surround a miscelle of ferric hydroxyphosphate. A single ferritin molecule can contain as many as 4,000 molecules of iron (as Fe^{+3}) and almost 50% of the weight of ferritin can be iron. Under typical conditions of iron balance, about 23% of ferritin is iron.

If cellular iron levels increase, the iron can bind to the mRNA for apoferritin and increase its translation to protein. This is important in the intestinal mucosal cells as increased iron absorption results in increased apoferritin synthesis and consequent increased storage as ferritin (& then loss with sloughing of the enterocyte) rather than the excess iron passing into the plasma.

The liver is the major site where iron is stored (as ferritin) in the body but many cells including those in the spleen and bone marrow also contain ferritin. Reticuloendothelial macrophages are another major ferritin store. When there is a demand for iron in the body, the transferrin saturation falls and increased amounts of transferrin are synthesised in the liver. Iron (Fe^{+3}) is released from ferritin and is converted to Fe^{+2} . The ferrous form binds to a transporter protein and crosses the cell membrane. Another copper containing ferrioxidase protein (caeruloplasmin) converts this to the ferric form which can bind to transferrin in the blood.

If iron stores are high, cells accumulate haemosiderin which is an insoluble cellular iron store composed of partially degraded ferritin.

How is iron carried in the blood?

Fe^{+2} is converted to Fe^{+3} and the Fe^{+3} is carried on the plasma protein transferrin. Transferrin is a β 1-globulin which is produced in the liver.

How is haem synthesised?

How and in what form is iron incorporated into haem?

Haem is the prosthetic group in haemoglobin, cytochromes and other proteins collectively referred to as haemoproteins. It is an iron containing tetrapyrrole consisting of 4 rings joined by methenyl bridges. Its synthesis consists of a series of reactions of which the first step is the condensation of glycine and succinyl CoA in a reaction with pyridoxal phosphate (vit B6) as a cofactor. This first step catalysed by ALA synthase is the important rate limiting step. This enzyme also has a short half-life (1 hr). Negative feedback control is exerted at this level in two ways:

- Synthesis of ALA synthase is greatly decreased by haem
- Activity of ALA synthase is greatly decreased by haem.

[The activity of this enzyme can be increased by barbiturates and this is of concern to anaesthetists in patients with an inducible porphyria (eg variegate porphyria).]

In the final step of the reaction sequence, ferrous iron is chelated with protoporphyrin IX to form haem in a reaction catalysed by ferrochelatase. [Note: ALA is δ -amino laevulinic acid.]

How much iron is required during pregnancy?

What happens to this increased iron uptake?

The adult female has a total body iron store of 2 to 2.5 g. Iron requirements increase by 1g during pregnancy. From about 20 weeks on, the mother takes up 6 to 7 mg of iron/day. By late in the third trimester, the foetus is taking up 4 mg/day from the mother.

Quantitatively, the major use of iron in the foetus is for synthesis of foetal haemoglobin, but it is also necessary for synthesis of other essential haem-proteins (eg cytochromes).

How does iron cross the placenta to the foetus?

Is this transport down a concentration gradient?

Iron crosses the placenta *against* a concentration gradient.

The process involves:

- release of iron from circulating maternal transferrin in the intervillous sinuses
- uptake of Fe^{+3} -transferrin by transferrin receptors in the membrane of trophoblast cells
- transport across the placenta
- release into the umbilical capillaries
- combination with foetal transferrin in the foetal circulation

The foetus is extremely efficient at taking up maternal iron. The foetal uptake of iron from the mother is not particularly affected by maternal iron deficiency unless very severe.

In what ionic form is the iron in 'reduced haemoglobin'?

'Reduced haemoglobin' is another term for deoxyhaemoglobin. The term 'reduced' here is used in the sense that loss of oxygen from a molecule is called 'reduction'. By common usage then when oxyhaemoglobin gives up oxygen it becomes 'reduced haemoglobin'. The form of iron in the haem of *both* oxyHb and deoxyHb is Fe^{+2} which is the reduced form of iron. Oxidation involves loss of electrons and Fe^{+2} loses an electron to become Fe^{+3} (the oxidised form of iron). Methaemoglobin is produced when the haem iron of haemoglobin is oxidised to the ferric form. Note the potential for confusion here as there are two different uses of the term 'reduced' when referring to haemoglobin. The term may be used to refer to the ionisation state of the haem iron (the ferrous form) or to deoxyhaemoglobin.