25. Iron

Physiology and metabolism

Iron is present in all cells in the body and has several vital functions: as a carrier of oxygen to the tissues from the lungs, in electron transport in cells and as an integral part of important enzymes.

The main part (>65%) of the iron in the body is present in the red cells as haemoglobin. In average adult men and women, approaching 3 mg and 2 mg iron respectively is in the form of haemoglobin. Myoglobin, the oxygen reserve in muscle, amounts to about 10% of the body iron. Iron is the functional portion of the cytochromes, essential for harnessing the energy of metabolized foodstuffs, and it is present in enzymes which play other key roles, for example, as signal-controlling substances, in some neurotransmittor systems in the brain such as the dopamine and serotonin systems. The amount of iron in cytochromes and enzymes is small.

The body has three unique mechanisms for maintaining iron balance and preventing iron deficiency and iron overload.

1. Storage of iron. Ferritin is a protein adapted for the reversible storage of iron. Iron stores are especially important for women to meet the excessive iron demands in the last trimester of pregnancy. The amount of stored iron is about 500-700 mg in 25-30 year old men. In women the amounts are much less. In most European countries at least 20-30% of women in the fertile ages have no iron stores at all.

2. Reutilization of iron. Iron is not lost from the body with urine or faeces but only with losses of cells, including bleeding. Iron is required to cover such losses and to supply the body with the needs for growth, including pregnancy.

3. Regulation of iron absorption. The body tries to maintain iron balance not by regulating the losses of iron but by controlling the absorption of dietary iron. This control is not perfect but still of great importance for the prevention of iron deficiency and excess [1].

Deficiency

When less iron is absorbed than is needed to cover iron losses and demands for growth and pregnancy, body iron stores, if present, are first depleted. When the stores are exhausted the supply of iron to various tissues is compromised. Iron deficiency can thus be defined as a state with an absence of iron stores. This state can be recognized clinically by the absence of stainable reticular iron in bone-marrow smears or more conveniently by a low serum ferritin (e.g. $\leq$15 g/L). The insufficient supply of iron to tissues depresses erythropoiesis. The haemoglobin level is reduced and at a certain point falls below the lower normal limit of the population. This is the rather arbitrary definition of iron-deficiency anaemia.

During the depletion of iron stores the absorption of iron increases, but if losses are high this compensatory mechanism may not be sufficient to guarantee an adequate delivery of iron for the formation of haemoglobin and enzymes.

A number of adverse effects of iron deficiency are known in man [2]. It was observed by early investigators that iron deficiency impaired physical endurance and work capacity. In recent years other functional defects have been demonstrated, such as disturbances in normal thermoregulation and impairment of certain key steps in the immune response. Great interest today is focused on the relationship between mild iron deficiency and various brain functions, such as learning. Iron is present in key enzymes in several neurotransmittor systems in the brain, for example, the dopamine and serotonin systems. Only 10% of the iron content of the brain is present at birth, 50% at the age of 10 and it continues to increase up to the age of 20-30 years. Studies in both children and animals strongly suggest that some of the brain symptoms are not reversible by iron treatment, even though all other signs of iron deficiency disappear. Emphasis should therefore be put on prevention rather than on treatment of iron deficiency [3-6].

Iron deficiency is probably the most frequent deficiency disorder in the world and the main remaining nutritional deficiency in Europe. In European countries the prevalence of iron deficiency as indicated by absence of iron stores is especially high in menstruating women and teenagers (about 20-30%). The prevalence of detectable anaemia due to iron deficiency is however much lower in these groups (around 2-8%).

Excess

The very effective regulation of iron absorption prevents overload of the tissues by iron from a normal diet, except in individuals with genetic defects as in idiopathic haemochromatosis.

Side effects of iron supplements

All iron compounds used therapeutically have side effects. The most disturbing side effects (epigastric pain, nausea and diarrhoea) are dose related and more severe if tablets are not taken with food. Other side effects such as constipation occur in some subjects but are independent of dose. Effects may be seen in adults with doses as low as 30 mg of elemental iron but most subjects tolerate well single doses of 100 mg.

Acute accidental iron intoxication is mainly seen in children who have mistaken iron tablets for sweets. The lowest known lethal dose in infants is 650 mg ferrous iron.

Physiological requirements (absorbed requirements)

Iron is needed to cover the basal losses of iron in cells shed from the body, to replace that lost by menstruation and to provide the amounts required for growth, including pregnancy.

The basal iron losses with cells from the exterior and interior surfaces of the body amount to 14 μg/kg body weight/d and are thus little over 1 mg/d in an average man and about 0.9 mg/d in an average woman [7] (see Table 25.1). The evidence suggests that these losses may have an interindividual variation of 15% (coefficient of variation). Sweat iron losses amount to only about 23 μg iron per litre of sweat and are thus so small that they can be disregarded [8].

Adult men and postmenopausal women

In healthy adult men and postmenopausal women, recommendations are derived from the basal iron losses. For an average adult man, the mean basal losses can be taken as 1.05 mg/d. The mean + 2SD would be 1.37 mg, which can be rounded off to give 1.4 mg/d. For an average postmenopausal woman, the corresponding figures will be 0.87 mg/d and 1.1 mg/d (Table 25.1).

Menstruating women

For women in the fertile age period the iron required to cover losses from menstruation has to be added. Menstrual iron losses vary markedly between women but are very constant in an individual woman. The magnitude of the menstrual losses is strongly genetically controlled and studies made in different countries report very similar figures for average menstrual losses when related to body size. An extensive study on menstrual blood losses in women at different ages was made in Sweden [9] (before contraceptive methods known to markedly influence the menstrual blood losses were introduced). The observed blood losses were transformed to iron losses by "multiplying" them by the distribution of the haemoglobin values in healthy women with optimal values. This is done by a mathematical-statistical process of convolution. The total iron requirements and their variation in menstruating women are then obtained by "adding" basal iron losses and their variation to the observed variation in menstrual iron losses by a further convolution step.

By this means the values in Table 25.1 were calculated. Table 25.2 shows the percentage of a population of menstruating women whose requirements are satisfied by various amounts of absorbed iron [10]. The 90th and 95th centile values of total absorbed iron requirements are 2.37 and 2.94 mg respectively.

Pregnancy and lactation

Pregnant women need iron to replace the basal iron losses during pregnancy (about 240 mg), to provide for the fetus and placenta (about 350 mg), and for the expansion of the red cell mass of the mother (about 450 mg). In total these requirements have been estimated as 1,040 mg [11]. The average blood loss at delivery corresponds to 250 mg iron. About 200 mg of the iron used for the expansion of the red cell mass is thus retained by the mother in her iron stores at delivery.

In the first trimester the iron requirement of the fetus is negligible. The total iron requirements of the mother are thus limited to the basal iron losses, about 0.9 mg/d. In the latter half of pregnancy iron requirements increase continuously and considerably, especially in the third trimester when the daily iron requirements reach the range 8-10 mg/d. Iron absorption is reduced in the first trimester but increases during the later half of pregnancy. In this period the iron requirements, however, are so great that, in spite of the increase in absorption, even on a diet with a good bioavailability there will be a deficit of about 400-500 mg iron. The physiological solution for covering the high iron requirements in pregnancy is to use iron from stores. The problem, however, is that very few women, if any, have iron stores of this magnitude. Therefore, daily iron supplements are recommended in the latter half of pregnancy [12]. Since diet alone cannot cover the iron requirements in most women, in their recent report [13] FAO/WHO refrained from giving a value for a recommended dietary intake during pregnancy.

Breast milk contains 0.15-0.3 mg iron/d. As menstruation is usually absent during lactation the total iron requirements in a lactating woman are considerably less than in an average non-pregnant, menstruating women.

Adolescent girls

Menstrual iron losses in teenage girls are about the same as in adult women [10]. Thus in menstruating teenage girls the requirements for growth and their variation have to be added to the requirements of adult menstruating women. This addition has also to be made using the same mathematical convolution process. There is a marked variation in growth rate in girls. The coefficient of variation of the change in body weight in the age range 13-16 years is about $\pm$ 19%. In the present calculations, the figures 0.36 $\pm$ 0.054 mg (mean $\pm$ SD) have been used as the daily amount of iron needed for growth [14]. This corresponds to the situation in 15-16 year old girls. In younger teenagers the growth requirements are higher (> 0.5 mg/d) but basal losses are then slightly lower. Moreover, some of the younger teenage girls have not started to menstruate. The growth figures used are based on a longitudinal study on the development of children [14] and on calculations of iron requirements for growth in the recent FAO/WHO report [13].

Table 25.2 shows the percentages of teenage girls whose needs are satisfied by various amounts of absorbed iron [10]. The 90th and 95th centile values for these girls are 2.54 and 3.10 mg/d respectively.

Adolescent boys

During the age period 12 to 16 years boys gain an average of 5.5 kg/year [14]. At the peak year of their growth spurt the average weight gain is about 10 kg. At about the same time, in response to sexual maturation, their haemoglobin concentration increases between 5-10 g/L per year. The 95th percentile value for total iron requirements may thus be considerably higher at the peak growth rate than the value given in Table 25.1. It should also be noted in Table 25.1 that the median iron requirement in adolescent males is as high as in adult menstruating women.

Children

Iron requirements in term infants are negligible for the first 4-6 months of life since there is a physiological redistribution of iron from the large red cell mass at birth to stores. This excess iron covers the needs for growth including expansion of the blood volume during this period. In the following months, however, the requirements are very considerable and amount to about 0.7 mg/d during the remaining part of the first year. This figure is very high in relation to body weight and energy intake.

The bioavailability of iron in weaning foods consumed during the age period 6-11 m is usually lower than that of iron in the adult diet because of an often high content of inhibitors of iron absorption such as milk and phytate in infant cereals and a low content of enhancers of iron absorption such as meat and ascorbic acid. The figure given for bioavailability in Table 25.1 (10%) may thus have a considerable variation. Moreover the bioavailability of iron used to fortify infant foods is usually unknown.

As shown in table 25.1 iron requirements are high in children especially in relation to their usual energy requirements and in periods of rapid growth. It is thus important that the bioavailable nutrient density for iron [15] is high in the diets of children.

Dietary iron requirements

Two main factors need to be considered in the translation of absorbed (physiological) iron requirements into dietary iron requirements: body iron status and composition of the diet.

Iron status and iron absorption

The absorption of iron from the diet is influenced by the iron status of the body: the greater the body's need for iron, the higher the percentage of a given dose taken up [16]. How this regulation mechanism works is unknown, but it is located in the intestinal mucosal cell. There is however an upper limit to this adaptation.

Dietary iron requirements must therefore be given for a certain iron status, and the calculations made here are based on the bioavailability of dietary iron at the borderline between normality and iron deficiency. The values given represent the amounts of iron needed to be absorbed to prevent an insufficient supply to tissues in the body, including the erythron, i.e. to maintain optimal haemoglobin values, but not iron stores.

Factors influencing dietary iron absorption

There are two kinds of iron in the diet with different absorption mechanisms: haem and non-haem iron [17]. Haem iron in meat and meat products amounts to about 1-2 mg/d in most EC countries and about 25% of haem iron present in meat is absorbed. This absorption is almost independent of meal composition and iron status.

Non-haem iron (in bread and other cereal products, vegetables and fruits) constitutes about 90% of the dietary iron intake. The dietary absorption of non-haem iron, however, is very dependent on iron status and the balance between several dietary factors influencing absorption. Some substances enhance the absorption of non-haem iron (e.g. ascorbic acid, meat, fish) and others inhibit it (e.g. phytate, calcium and iron-binding phenolic compounds). There is thus a marked variation in the absorption of iron from different meals depending on the meal composition.

Bioavailability of dietary iron

The bioavailability of iron from the diet as a whole needs to be known in order to translate absorbed iron requirements into dietary requirements. Direct information is limited as long-term chemical balance studies on different diets would be required. Indirectly, however, it is possible to estimate the bioavailability of iron in the whole diet using results obtained in different studies.

In a recent paper attempts were made using indirect methods to estimate the bioavailability of dietary iron in USA and different countries in Europe [10]. The calculations were made for iron-replete subjects with no iron stores. The estimated upper limit was about 15% of the intake of available iron and the figures were very similar in all studies after corrections were made for unavailable fractions of fortification iron [18]. This figure may represent "an average European diet" - rather varied, and containing meat, fish, bread, vegetables, fruits, etc. Diets with a very high meat intake (>250 g/d) may have a slightly higher bioavailability, possibly amounting to 17%, whereas diets with little red meat (<50 g/d) and little fruit and vegetables with meals, or having a high phytate content due to a high consumption of cereal fibre (wholemeal bread, crispbread) may have a lower bioavailability, possibly down to 10% or even less. The bioavailability of iron in some vegetarian diets with a low content of ascorbic acid is thus probably much lower (5-10%). It is important to be aware of the multitude of factors influencing the bioavailability of iron and that there may be segments of most populations having diets with a rather poor bioavailability. On the other hand, for the European population at large, the error will not be great if a single figure of 15% is selected as a basis for the calculations of dietary requirements from the physiological requirements.

The present figure for bioavailability of iron from the whole diet (15%) should be considered as the upper borderline value associated with maintenance of health (i.e. absence of iron stores but normal haemoglobin values). Correction should be made for dietary fortification iron that is only partially soluble in the gastrointestinal tract. For example, only about 15% of reduced iron, often used for fortification of flour, is potentially available [18]. It can then be estimated that 15% of this fraction will finally be absorbed.

Values proposed

The values given in Table 25.1 are the intakes needed to cover the requirements of 95% of the various population groups, based on a bioavailability of 15%.

Menstruating women, both adults and teenagers, have a very skewed distribution of their iron requirements. A PRI based on the 95th centile would be unrealistically high for the great majority of women, so Table 25.1 gives the requirements of the 90th and 95th centiles of menstruating women.

Table 25.2 gives the physiological requirements and dietary intakes needed to cover centiles of the population of menstruating women from the 50th to the 95th.

Strategies to improve iron nutrition

Modification of dietary composition

Iron nutrition can be improved by various modifications of the diet. A higher intake of foods enhancing iron absorption or a lower intake of foods inhibiting absorption (see earlier) will increase the bioavailability of the dietary iron.

An increased intake of lean meat will not only provide more well-absorbed haem iron but also enhance the absorption of non-haem iron. The latter can also be achieved by increasing the intake of ascorbic acid-rich foods, especially if the usual intake of ascorbic acid is low.

Iron supplementation

The iron balance situation for most women is critical during pregnancy. With the present type of diet and present low-energy life-style about 500 mg iron would be needed in iron stores of mothers to cover iron requirements during pregnancy. About 25-30% have no iron stores; the average store is about 150 mg; less than 5% reach an amount of 400 mg and none the critical amount of 500 mg. This is the background for the FAO/WHO recommendation [13] that all pregnant women should be given iron supplements during the latter half of pregnancy.

Iron fortification

The marked skewness of the distribution of iron requirements in menstruating women implies that a considerable fraction of them are at risk of developing iron deficiency. Personal assessment of individual menstrual losses is unreliable and women with physiological but heavy losses usually consider themselves as quite healthy and their losses as normal. They would not seek medical advice and thus cannot be simply reached and given iron supplementation. Iron fortification is then a measure that must be seriously considered, especially as the life style of many individuals results in their having low energy needs, and thus reduced food consumption, resulting in a lowered iron intake.

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Table 25.1 Absorbed and dietary iron requirements [a].

Age	Mean body weight	Growth requirements	Basal losses	Menstrual losses		Total requirements		Dietary iron requirements (assuming bioavailability 15%)			
years	kg	mg/d	Median mg/d	Median mg/d	95th per. mg/d	Median mg/d	95thper. mg/d	mg/d (rounded to nearest mg/d in brackets)			
								90th centile		95th centile	
0.5-1	9	0.55	0.17			0.72	0.93			[6.2] b	(6)
1 - 3	13.5	0.27	0.19			0.46	0.58			3.9	(4)
4 - 6	19.5	0.23	0.27			0.50	0.63			4.2	(4)
7 - 10	29	0.32	0.39			0.71	0.89			5.9	(6)
Males 11 - 14	44.5	0.55	0.62			1.17	1.46			9.7	(10)
15 - 17	62	0.60	0.90			1.50	1.88			12.5	(13)
18+	75		1.05			1.05	1.37			9.1	(9)
Females 11 - 14 d	45	0.55	0.65			1.20	1.40			9.3	(9)
11-14	45	0.55	0.65	0.48 c	1.90 c	1.68	3.27	18	(18)	21.8	(22)
15 - 17	54	0.35	0.79	0.48 c	1.90 c	1.62	3.10	16.9	(17)	20.7	(21)
18+	62		0.87	0.48 c	1.90 c	1.46	2.94	15.8	(16)	19.6	(20)
Post-menopausal women	62		0.87			0.87	1.13			7.5	(8)
Lactating women	62		1.15			1.15	1.50			10	(10)

a. Partly based on an FAO/WHO report [13] and partly on new calculations of the distribution of iron requirements in menstruating women [10]. Because of the very skewed distribution of iron requirements in these women, dietary iron requirements are calculated for two levels of coverage, 90% and 95%, in these groups.

b. Bioavailability of dietary iron during this period is greatly varying and on average lower than 15%. With a 10% bioavailability, for example, dietary iron requirements will be 9.3 mg.

c. Effect of the normal variation in Hb concentration not included in this figure.

d. Non-menstruating

Table 25.2 *The percentages of populations of menstruating adult women and girls aged 15-17 years whose needs will be satisfied by various amounts of absorbed iron, and the dietary intakes that would be necessary to provide these amounts, assuming 15% bioavailability.*

Probability of adequacy	Absorbed iron requirements (mg/d)		Dietary iron intake (mg/d)	
%	Adult women	Adolescents	Adult women	Adolescents
50	1.46	1.62	9.7	10.8
55	1.51	1.68	10.1	11.2
60	1.58	1.75	10.5	11.7
65	1.65	1.81	11	12.1
70	1.74	1.90	11.6	12.7
75	1.83	2.00	12.2	13.3
80	1.96	2.12	13.2	14.1
85	2.12	2.29	14.1	15.3
90	2.37	2.54	15.8	16.9
95	2.94	3.10	19.6	20.7