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IRON DEFICIENCY

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INTRODUCTION

A nutritional deficiency of iron develops when the amounts absorbed from the diet by the gastrointestinal tract are insufficient to meet normal requirements. Food iron absorption is a function of dietary composition. While the overall iron content of diets remains relatively constant, differences in composition account for wide variations in bioavailability. This review discusses several topics, including the assessment of iron storage status, iron losses and requirements, food iron absorption, and the prevalence, biologic consequences, and prevention of iron deficiency.

ASSESSMENT OF IRON STATUS

There are different degrees of iron deficiency (11). The mildest manifestation is a reduction of iron stores. When stores have become totally exhausted, less iron is delivered to the transferrin of plasma and, as a consequence, the erythroid marrow becomes depleted of iron. The final and most severe manifestation is an anemia in which the red cells are microcytic and hypochromic. Diagnostic measurements can be divided into those that assess iron stores and those that reflect the availability of iron to the erythroid marrow. The former measurements include the histologic assessment of reticuloendothelial iron stores in the bone marrow and the serum ferritin and transferrin concentrations; the latter include the saturation of transferrin, free erythrocyte protoporphyrin content, mean red cell volume, hemoglobin concentration, and serum concentration of circulating transferrin receptors.

Size of Iron Stores

The absence of bone marrow hemosiderin in reticuloendothelial cells is regarded as the most accurate indicator of iron deficiency (21); such measurements, however, are clearly not appropriate for population studies. Of much more practical value is the serum ferritin concentration, which bears a semiquantitive relationship with body iron stores in the concentration range of 20 to 200 μg per liter; 1 μg per liter serum ferritin is roughly equivalent to 8 mg storage iron (21, 114). A low serum ferritin concentration (< 12 μg per liter) is significant, since it is virtually diagnostic of iron deficiency (101). The serum ferritin loses its diagnostic value in the presence of infection, inflammation, ineffective erythropoiesis, malignancy, and liver disease, all of which result in higher serum concentrations (76).

While the serum transferrin concentration rises in people with iron deficiency as a consequence of enhanced hepatic synthesis (90), it is not a sensitive indicator of iron deficiency, since one third of anemic patients responding to iron treatment have transferrin concentrations in the normal range (2).

Measurement of Iron Supply to the Erythroid Marrow

The serum iron concentration is low in iron-deficient people. It is, however, a relatively unreliable index of iron nutrition, since it is modified by a number of other factors (11). As a result, the degree to which transferrin is saturated with iron also has limitations when used on its own. A saturation of less than 16% is nevertheless useful when interpreted in combination with other iron measurements. It is noteworthy that iron-deficient red cell precursors express greater numbers of receptors for transferrin on their surfaces, and fragments of these receptors circulate in the plasma in increased quantities in iron deficiency (49, 68). The relative diagnostic value of this exciting finding awaits elucidation.

As the iron supply to erythroid precursors becomes progressively curtailed, there is a corresponding rise to > 70 μg per deciliter in the concentration of free erythrocyte protoporphyrin in maturing red blood cells. Such a rise, however, is not specific to iron deficiency and is found also in lead poisoning, the anemia that accompanies chronic disease, and thalassemia. The reduction in the iron supply to the erythroid marrow leads to a progressive drop in the hemoglobin concentration. To define the cutoff value for normality in population studies poses a problem, because there is significant overlap between iron-deficient subjects and normal subjects with hemoglobin concentrations at the lower limits of normal (22). In established iron-deficiency anemia the red cells are small (< 80 fL). Similar reductions in the mean red cell volume occur in other conditions associated with impaired hemoglobin synthesis, including the anemia of chronic disorders, thalassemia, and sideroblastic anemia.

Use of a Combination of Measurements

While single measurements are of limited value as predictors of iron-deficiency anemia, their specificity is significantly increased when two or more are abnormal (23, 43). A more sophisticated approach has been developed recently for population studies (30). Several iron measurements are used jointly to estimate the total body iron content in individual subjects and to assess changes in the iron status of population samples. The usefulness of this approach has recently been confirmed in a fortification trial in South Africa (4).

Quantitative Aspects of Iron Losses

THE INFANT A normal full-term infant has a minimal daily dietary requirement of 0.3 mg iron, and a premature infant requires significantly more iron (14, 20). Growth in the second year of life increases the daily requirement in infancy to 0.4 mg. Thereafter, iron requirements steadily rise to about 1.6 mg per day during the adolescent growth spurt. In late adolescence and early adulthood the daily requirement drops to 1.2 mg in men.

THE ADULT MAN Basal obligatory losses of iron in the adult man occur predominantly from the gastrointestinal tract, skin, and urinary tract (0.6 mg, 0.3 mg, and <0.1 mg per 24 hr, respectively) (54). These losses are regulated in relation to iron storage status but within a narrow range (11). Claims that significant amounts of iron can be lost in sweat have not been confirmed in a recent study (13).

THE ADULT WOMAN Median monthly menstrual blood loss in the adult woman is between 20 and 30 ml. This loss increases median daily requirements from a basal figure of about 0.8 mg to 1.3 mg in a 55-kg woman. The ceiling iron loss for 95% of normal menstruating females is approximately 1.6 mg per day, which translates into a total daily iron requirement of 2.4 mg per day (11). Methods of contraception markedly influence iron losses. Oral contraceptives reduce losses by about 50%, whereas intrauterine devices increase losses by up to 100%.

PREGNANCY Approximately 1000 mg iron is needed by a 55-kg woman during a normal pregnancy. This requirement includes 230 mg for basal losses, 450 mg for an increased red cell mass, 270 to 300 mg for the fetus, and 50 to 90 mg for the products of conception (11, 56, 65). Since the greatest increase in fetal and erythropoietic requirements occurs later in gestation, the major requirements (5 to 6 mg per day) are in the second and third trimesters. The iron present in the expanded red cell mass is returned to stores postpartum, but this recovery is partially nullified by iron lost with peripartum blood loss (56). The total iron loss during pregnancy may be reduced substantially in developing countries, where the increase in red cell mass is limited by lack of available iron and where maternal and fetal weights are lower than in more highly developed countries. A period of amennorhea occurs postpartum, but iron losses via lactation are roughly equivalent to losses incurred via menstruation.

PATHOLOGIC LOSSES Epidemiologically, the most important pathologic losses of iron occur with hookworm infestation, which affects as many as 450 million people. It has been calculated that infestation with *Necator americanus*, (~5000 eggs per gram of feces) increases the daily iron requirement by 3–4 mg (75). It should, however, be emphasized that the hookworm load is small in the majority of subjects living in endemic areas and that other factors, such as the poor bioavailability of dietary iron, contribute to the widespread prevalence of iron-deficiency anemia in endemic areas.

Recommended Daily Intakes of Dietary Iron

Recommendations are that normal infants receive 1 mg iron per kg per day and that low-birth-weight infants receive 2 mg iron per kg per day (20). Such

requirements can be met only by fortification of infant formulas. The recommended amounts for children and male and female adolescents are 10, 12, and 15 mg per day, respectively (64). For women during the reproductive years; 15 mg per day is recommended and adult men and postmenopausal women require only 10 mg per day. The requirements of women in the second and third trimesters of pregnancy (5 to 6 mg per day) cannot be met by any diet, and supplemental elemental iron (30 mg per day) is required.

While these are useful guidelines, they do not allow for the considerable variations in the bioavailability of iron in different diets. In this context, significant numbers of apparently well people in more highly developed countries consume significantly lower amounts of iron than the recommended daily intake (5).

FOOD IRON ABSORPTION

The amounts of iron absorbed from the gut are determined by the food iron content, the composition of the ingested food, and the ability of the gastrointestinal tract to absorb iron.

Food Iron Content

Typical Western diets have a remarkably consistent iron content of approximately 6 mg per 1000 kcal. The major determinants of the absorption of this iron are the particular sources of iron within the meal. The iron in food is present either as heme or nonheme compounds. Heme iron is efficiently absorbed via specific, high-affinity, mucosal brush-border heme-binding sites (53). While absorption of heme iron is not influenced by the promoters and inhibitors of nonheme iron absorption (70, 81), it is enhanced by dietary protein, digestion products of which prevent the formation of poorly absorbed heme polymers (81). The bioavailability of the heme iron in meat is excellent. In contrast to heme iron, the absorption of the nonheme iron in food is profoundly influenced by the interplay of a number of enhancing and inhibitory iron-binding ligands in different diets (17). While most nonheme iron in the diet enters a "common pool" insofar as absorption is concerned, certain dietary components, such as ferritin and hemosiderin, are very poorly absorbed. Various forms of iron that often contaminate the diet in developing countries are also poorly absorbed (57, 74). As a result, the dietary iron content in these regions does not necessarily reflect the amount of bioavailable iron.

Food Composition and Iron Bioavailability

The absolute iron content of a diet is less important in terms of bioavailability than is the composition of the diet. This section highlights the major factors that modify nonheme iron bioavailability.

ENHANCERS OF NONHEME IRON ABSORPTION Not only does meat contain highly bioavailable heme iron, but it also can enhance nonheme iron absorption even from meals of low bioavailability (8, 72). This important property, which relates specifically to meat protein (8, 26), may involve the release of cysteine (73), cysteine-containing peptides (73, 105), and other peptide digestion products (67), or interaction with the carboxyl groups of amino acids (100). Current data suggest that 1 to 1.5 g meat is equivalent to 1 mg ascorbic acid (61, 89) in its ability to promote nonheme iron absorption.

Ascorbic acid is the most powerful promoter of nonheme iron absorption (3, 41, 52, 58, 99). It both reduces and binds dietary nonheme iron. A plot of the absorption of food iron against the molar ratio of ascorbic acid to iron yields a biphasic curve; a relatively greater ascorbate effect occurs with ratios <7.5 (80). The absolute effect of ascorbic acid in a particular meal depends on the relative proportion of ligands that promote or inhibit iron absorption (58). Prolonged heating leads to the inactivation of ascorbic acid. Nonheme iron absorption is also promoted by citric, malic, tartaric, lactic, and other organic acids. Citric acid promotes iron absorption from a number of fruits, including citrus products (3), and lactic acid promotes iron absorption from fermented cereal beers (42) and sauerkraut (52). Certain spices (69) and fermentation products of the soybean (85) have recently been shown to have promoting activity.

INHIBITORS OF NONHEME IRON ABSORPTION Polyphenols are secondary plant metabolites that are rich in phenolic hydroxyl groups (15). Both the hydrolyzable and nonhydrolyzable (condensed) polyphenols inhibit nonheme iron absorption (44, 52). The first polyphenols shown to have such an effect were the tannins in tea (44). Subsequent studies showed polyphenols in vegetables, such as sorghum and legumes, and in certain condiments to be powerful inhibitors of nonheme iron absorption (52, 97). The effect is dose related, with a near maximal inhibition of absorption ($\pm$ 75%) at doses of $\sim$50 mg.

Phytates constitute 1 to 2% (by weight) of many cereals, nuts, and legumes and represent the physiologic phosphorous storage mechanism of these plants (19). The bulk of in vivo evidence indicates that phytates inhibit dietary iron bioavailability (52, 62); 50 mg of phytates cause a reduction in dietary iron absorption of $\sim$70% (60, 62).

Unlike proteins in meat, the plant proteins in soybeans, nuts, and lupines inhibit iron absorption (27, 40, 83–85). In vitro data suggest that high-molecular-weight peptides may be the inhibitory factors (67). Calcium and phosphorous, when fed together, inhibit food nonheme iron absorption (88). While data show that fiber components can inhibit iron bioavailability, there is no evidence that the intact dietary fiber complex inhibits iron absorption (1, 28, 46, 51).

Nutritional Implications of Dietary Composition

Individual foods can be divided into three categories based on their effects on the bioavailability of iron in the diet: low, medium, or high bioavailability (Table 1) (9, 89). The fact that the ultimate absorption of iron from any particular meal is the result of a complex interplay of promoting and inhibitory factors makes accurate predictions of the bioavailability of iron from a particular meal difficult. Certain general conclusions can be reached, however. A diet of low bioavailability (5% absorption in a subject with depleted iron stores) is a simple monotonous diet of cereals, roots, or tubers with negligible quantities of meat, fish, or ascorbic acid. This diet inhibits

Table 1 Relative bioavailability of iron in the presence of various dietary components

Dietary components	Bioavailability of iron		
	Low	Medium	High
Cereals	Maize	Corn flour	
	Oat meal	White flour	
	Rice		
	Sorghum		
	Whole wheat flour		
Fruits	Apple	Cantaloupe	Guava
	Avocado	Mango	Lemon
	Banana	Pineapple	Orange
	Grape		Papaya
	Peach		Tomato
	Pear		
	Plum		
	Rhubarb		
	Stawberry		
Vegetables	Aubergine	Carrot	Beetroot
	Butterbean	Potato	Broccoli
	Broadbean		Cabbage
	Lentil		Cauliflower
	Spinach		Pumpkin
			Turnip
Nuts	Almond		
	Brazil		
	Coconut		
	Peanut		
	Walnut		
High-protein foods	Egg		Fish
	Isolated soy protein		Meat
	Soy flour		Poultry

food iron absorption and is typical of diets consumed in the developing world. Such a diet supplies only ~0.7 mg of iron daily and clearly is insufficient to meet requirements in women and many men. An intermediate diet (10% absorption) contains some meat, fish, or ascorbic acid–containing food in addition to the previously mentioned constituents. Such a diet supplies ~1.4 mg iron daily, which is adequate for the needs of 50% of women. A diet of high bioavailability (15% absorption) contains generous quantities of meat, poultry, fish, and ascorbic acid. Such a diet is consumed by most segments of the population in industrialized countries. It supplies more than 2 mg iron daily, which meets the requirements of most adults.

Intestinal Mucosal Behavior

The capacity of the intestinal mucosa to absorb iron is inversely related to the iron-storage status of the individual subject (12, 24). The mucosa normally adapts efficiently to changing body needs, but occasionally it may be a contributory factor to the development of nutritional iron deficiency in areas where small bowel disease, such as tropical sprue, occurs.

PREVALENCE OF IRON DEFICIENCY

Using WHO criteria for the diagnosis of anemia (113), valuable data have been published recently on the prevalence and geographic distribution of anemia worldwide (39). An estimated 30% of the world's population (i.e. 1.3 billion people) are anemic, with the highest prevalence in developing countries. Young children and pregnant women are the most vulnerable, and south Asia and Africa are the most severely affected regions. Of all the causes of anemia, iron deficiency, which affects between 0.5 and 0.6 billion people, is by far the most frequent. In contrast, the iron nutrition of people in the more highly developed countries is much more satisfactory. The Second National Health and Nutrition Examination Survey (NHANES II) study in the United States revealed a low overall prevalence of anemia, with the highest incidence found in girls between the ages of 15 and 17 years (5.9%), followed by infants 1 to 2 years of age (5.7%) (35). In another United States survey specifically focussed on iron deficiency, the incidence in adult women dropped from 8.4% in 1978 to 2.3% in 1986 (30). Similar findings have been reported from Sweden (55). The relative contributions of economic prosperity, consumer habits, and iron fortification toward these improvements are not clear, but the fact that the incidence of iron-deficiency anemia in females has reportedly not changed in Japan, a country that engages in limited iron fortification (8.3% in 1972 and 8.4% in 1988) (106), is of interest.

BIOLOGIC CONSEQUENCES OF IRON DEFICIENCY

The most obvious result of iron deficiency is anemia, with all its well-known sequelae. Increasing evidence suggests, however, that iron deficiency also adversely affects other metabolic processes, including electron transport, catecholamine metabolism, DNA synthesis, and several enzyme systems (11, 25, 31, 66). Impairments in work performance, neurologic function, the immune response, and epithelial tissues have been attributed to iron deficiency.

Work and Exercise Performance

Data from animal studies indicate that iron deficiency, independent of anemia, produces specific enzymatic changes that lead to impaired endurance exercise performance (36, 47, 94). The endurance muscle fibers are selectively affected (86). The extent to which these findings are applicable to humans, however, is still not clear. Although iron-deficiency anemia has been shown to impair work performance in studies of both short-term exercise (7, 18, 50, 109) and more long-term manual labor (6, 45), it is difficult to distinguish between the effects of anemia per se and those of iron deficiency. Two attempts have recently been made to separate the two components. In one study, subjects were venesected to induce iron deficiency and then received transfusions to reverse the anemia rapidly without affecting the tissue iron deficiency (16). In the other study, work performance was assessed in subjects with polycythemia vera who had been rendered chronically iron deficient by venesection therapy (98). Neither study was able to demonstrate a disturbance of work performance that could be ascribed to a specific muscle defect.

Neurologic Function

Animals rendered iron deficient at an early age exhibit a depletion of brain iron and behavioral defects that are not totally corrected by iron administration (33, 34, 48, 111). Behavioral disturbances have also been noted in human infants with iron-deficiency anemia and are not reversible by use of either short-term (78, 79, 92) or more long-term treatment (78). In addition, follow-up studies of such children years later have reported the persistence of some behavioral abnormalities (38, 93, 102). In summary, reviews of current data indicate that iron-deficiency anemia has deleterious effects on neurologic function (77, 95) and that these effects may be only partially reversible. Iron deficiency without anemia has not been found to be associated with behavioral abnormalities (37, 78).

The Immune Response and Infection

Certain components of the immune response are disturbed in the presence of iron deficiency. Although the humoral component of the inflammatory response appears to be intact (25, 32), abnormalities have been described in cell-mediated immunity (32, 82, 96), in neutrophil function (91, 110), and in the secretory response of macrophages (63). The clinical significance of these findings is unclear, however. Indeed, whether predisposition to infection is the result of iron deficiency or iron-replacement therapy is not clear. Various explanations are given for these conflicting findings: inadequate diagnosis of iron deficiency, nonphysiologic forms of iron administration, the dependence of certain parasites such as malaria on adequate red cell numbers, nonrepresentative patient and control sampling, and socioeconomic variables (25, 32). Controlled clinical evaluation is urgently needed to resolve this issue.

Epithelial Tissues

The tissues of the gastrointestinal tract have been reported to be extremely sensitive to iron deficiency. However, glossitis, stomatitis, esophageal webs, and chronic gastritis may partly result from other coincidental deficiencies. Such manifestations are now rare, but atrophic gastritis has possible pathogenetic significance, since the resultant hypochlorhydria in itself limits nonheme iron absorption (11, 25, 31, 66).

PREVENTION OF NUTRITIONAL IRON DEFICIENCY

There are two approaches to iron deficiency: supplementation and fortification. Supplementation with pharmacologic amounts of oral iron is used to induce a rapid improvement in symptomatically deficient subjects and to prevent anemia in pregnancy. Fortification, on the other hand, seeks to improve the iron nutritional status of population groups on a long-term basis. Small amounts of iron are added to some staple dietary constituent and thus the compliance of individual subjects is not required. Since iron fortification represents the only potential way to address the global problem of iron-deficiency anemia, we briefly consider some of the principles involved in its application.

Iron Fortification

The choice of a suitable iron compound presents difficulties, since iron is highly reactive and can cause food discoloration and oxidative reactions. Ferrous sulphate is widely used in bread and bakery products because the storage time is usually brief. Ferrous salts are also employed in infant formulas. Elemental iron powder of small particle size has also been used in bread and flour fortification, but recent evidence indicates that one such

compound (carbonyl iron) is of low bioavailability (59). The chelator NaFeEDTA is stable and less susceptible to the inhibitory ligands present in cereal-based diets (71, 87). Another approach uses a relatively inert form of iron, such as iron orthophosphate, together with an enhancer of iron absorption (112).

The ideal vehicle should be processed centrally and consumed by the target population in fairly uniform quantities (29). It should have a brief storage period and should lend itself to the unobtrusive and inexpensive addition of the iron compound. The most commonly fortified vehicles in more developed countries are flour, infant cereals, and milk powder. For adequate absorption of iron these two latter vehicles should contain adequate amounts of ascorbic acid (42, 104).

Iron fortification is difficult in developing countries for a number of reasons. These include cost considerations, decentralized food production, and staple foods of low iron bioavailability that do not lend themselves to fortification. Several strategies have been employed in pilot fortification programs, including the use of NaFeEDTA as the iron compound and the use of sugar and condiments such as fish sauce, fish paste, and curry powder as the vehicles (4, 69, 71, 87, 108). In one novel approach, dried animal hemoglobin was baked into chocolate biscuits as part of a school lunch program (103).

Depending on circumstances, fortification programs can be applied nationally or targeted specifically at vulnerable groups (e.g. infants) (29). If a centrally processed dietary staple cannot be identified, then multiple regional programs may be necessary. Before embarking on such programs, the bioavailability of the fortificant iron from typical diets must be tested. Storage characteristics and consumer acceptability of the fortificant and the vehicle must also be established. If all preliminary tests are satisfactory, a pilot study can begin. In one recent study a targeted approach was successfully applied in which curry powder was the vehicle and NaFeEDTA the fortificant (4). Curry powder was chosen because it was widely consumed by the iron-deficient Indian population but not by blacks, in whom iron overload occurs commonly. In a double-blind trial conducted over two years, the prevalence of anemia in the group of women receiving fortification dropped from 22 to 5% (Figure 1).

Results of several field trials suggest that carefully planned iron-fortification programs are effective and safe (4, 29, 107). At a national level, however, pinpointing the individual reasons for improvements in iron nutrition is still difficult. For example, in Sweden hemoglobin levels of women have risen significantly in the recent past (55), despite evidence that the iron fortificant used in the diet is poorly bioavailable (59). Other factors that may have contributed include improvements in socioeconomic status, widespread

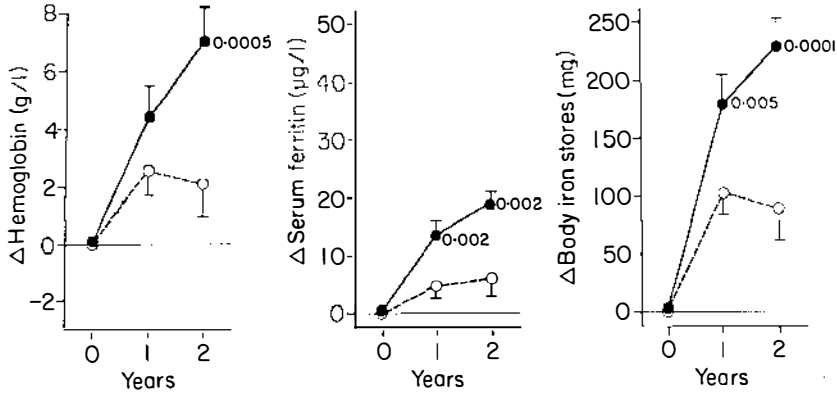

Figure *1* Changes in hemoglobin, serum ferritin, and calculated body iron stores (30) after one and two years in iron-fortified (*filled circles with solid line*) and control (*open circles with dashed line*) groups of Indian women. The fortificant was NaFeEDTA, and the vehicle was curry powder. Individual points represent mean changes ± SE. The probability (one tailed) using Student's *t* test that individual changes were greater in the fortified group than in the control group is also shown [data from D. E. Ballot and co-workers (4)].

consumption of over-the-counter iron and ascorbic acid tablets, and decreased menstrual losses due to the use of birth-control pills (55).

Questions remain about the potential hazards of increased iron fortification in whites because of the high gene frequency of the HLA-linked iron-loading gene, which can predispose homozygous carriers to clinical hemochromatosis (10). These doubts emphasize the need for careful monitoring in developed countries where iron fortification programs are in operation. While application of national fortification programs is widespread in more highly developed countries, where they are least needed, the absence of such programs in the developing world, where iron deficiency anemia is far more prevalent, is cause for concern.

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