Why Nutritional Iron Deficiency Persists as a Worldwide Problem[1,2]

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Abstract

The earliest studies of food iron absorption employing biosynthetically incorporated radioisotopes were published in the 1950s. Wheat flour has been fortified with iron in Canada, the United Kingdom, and the United States since the 1940s. However, half a century later, nutritional iron deficiency (ID) is estimated to affect 1.5–2 billion people worldwide. The reasons for the apparently limited impact of health and nutrition policies aimed at reducing the prevalence of ID in developing countries are complex. They include uncertainty about the actual prevalence of ID, particularly in regions where malaria and other infections are endemic, failure of policy makers to recognize the relationships between ID and both impaired productivity and increased morbidity, concerns about safety and the risks to iron-sufficient individuals if mass fortification is introduced, and technical obstacles that make it difficult to add bioavailable iron to the diets of those at greatest risk. It is, however, likely that the next decade will see a marked reduction in the prevalence of ID worldwide. More specific assessment tools are being standardized and applied to population surveys. The importance of preventing ID during critical periods of the life cycle is receiving increased attention. Innovative approaches to the delivery of bioavailable iron have been shown to be efficacious. The importance of integrating strategies to improve iron nutrition with other health measures, and economic and social policies addressing poverty as well as trade and agriculture, are receiving increasing consideration.   J. Nutr. 141: 763S–768S, 2011.

Introduction

Iron excretion is minimal and unregulated in human beings (1). Nutritional iron deficiency (ID)[3] occurs when the diet supplies insufficient bioavailable iron to meet the body's requirements for growth and pregnancy and to replace iron lost from the gastro-intestinal tract and skin, in the urine, and through menstruation.

The causes have been known for over 50 y. The major factors are poverty, because it limits dietary diversity, and the agricultural revolution that resulted in animal foods rich in bioavailable iron being displaced by cereals, legumes, and plant-based diets (2). The classical iron balance study carried out by Widdowson and McCance in 1942 (3) demonstrated that less iron was absorbed from bread with a high bran content than from white bread. The inhibitory role of phytate was suspected, because phytic acid was shown to inhibit iron absorption (4). Isotopic studies, first performed over 50 y ago, refined our understanding of the poor bioavailability of iron in cereal and other vegetable foods (5). The major enhancers of absorption, ascorbic acid and animal tissue, were also identified (6–8). A second major class of inhibitors, certain polyphenols, was discovered in 1975 (9,10). This large body of experimental work provided the basis for predicting dietary bioavailability (11,12) and designing effica-cious strategies for alleviating nutritional ID anemia (IDA) (13,14). Wheat flour has been fortified with iron in Canada and the United States since the 1940s (15) and the marked decline in the prevalence of IDA in infants and young children in industri-alized countries such as the United States is generally attributed in part to the fortification of infant formulas and weaning foods (16–18). Iron is also added to many processed foods, such as breakfast cereals, in Western countries. Finally, the efficacy of supervised iron supplementation is well established (19).

Despite a relatively clear understanding of the physiology of food iron absorption, ID is estimated to affect as many as 2

billion people (20). The reasons for the apparent discrepancy between our understanding of the scientific basis for nutritional ID and the fact that it remains a highly prevalent form of undernutrition worldwide are complex. They include questions about the accuracy of ID prevalence estimates, failure of policy makers to appreciate the severity of the consequences of ID, and programmatic and technical obstacles to the implementation of corrective measures. The following is a brief discussion of the most important issues and some potential solutions.

Assessment of Iron Status

Screening for ID in developing countries is usually based solely on hemoglobin (Hb) measurements (21). Sensitivity is low because the overlap in Hb concentrations between healthy and iron-deficient individuals is considerable, especially if the cutoff values used to identify anemia are not appropriately adjusted for age, gender, pregnancy, ethnicity, smoking, and altitude (22,23). Specificity is poor, because a multitude of disorders other than ID can cause anemia. They include other nutritional deficiencies (vitamins A and B-12 and folic acid), infections (notably malaria, HIV disease, and tuberculosis), and inherited disorders of erythropoiesis (such as the thalassemic syndromes and hemoglobinopathies). Considerable regional variability is present not only in the proportions of individuals with anemia who have ID but also in the proportions of individuals with ID who have IDA.

When used in conjunction with appropriate clinical information, specific iron indicators permit iron status to be determined accurately. However, specificity and sensitivity are considerably diminished when they are applied to population surveys. All of the indicators available at the present time are affected by factors other than ID that may remain undetected in random samples (**Table 1**). Serum ferritin (SF) is a quantitative measure of the size of body iron stores in health and uncomplicated ID (1). However, it is also an acute phase protein (24). Levels may not accurately reflect iron status in the presence of infection, inflammation, and liver disease. Serum iron, transferrin saturation, and RBC zinc protoporphyrin (ZPP) are indicators of the adequacy of the iron supply for developing RBC. Serum iron and transferrin saturation are decreased and RBC ZPP is increased in ID, but also in other conditions, such as inflammatory disorders, in which iron transport out of stores is limited. RBC ZPP is increased by environmental exposure to lead. Serum transferrin receptor (STfR) concentrations provide semiquantitative information about the size of any disparity between iron supply and erythroid bone marrow demand. The value is a semiquantitative measure of the size of the iron deficit in uncomplicated ID. It is less affected by inflammation than SF (25), but concentrations are increased in the presence of accelerated erythropoiesis resulting from hemolysis or ineffective erythropoiesis (26). The RBC indices [mean cell volume (MCV), mean cell Hb (MCH), and RBC distribution width (RDW)] are all abnormal in IDA (MCV↓, MCH↓, and RDW↑). However, MCV and MCH are also reduced in thalassemia and in some individuals with anemia caused by infection. Finally, the reticulocyte Hb concentration (CHr) is a measure of iron availability to RBC recently released from the bone marrow. It has been advocated as a tool for diagnosing ID and IDA in infants and young children (27) but is unlikely to be available in developing countries because of the cost of purchasing and maintaining automated hematology analyzers with this capability.

The use of combinations of indicators to improve the accuracy of estimates of the prevalence of ID in population samples was pioneered by Cook et al. (28) and was for many years the basis for estimating prevalence in the United States (29). Similar combinations of indicators have been employed in surveys in other countries. Skikne et al. (30,31) demonstrated more recently that the STfR:SF ratio can be used to semiquantitatively determine iron status in individuals with ID, normal iron balance, and increased iron stores. The latter method has several advantages. It does not rely on parameter cutoff values, it yields a measure of the size of the iron deficit that is independent of Hb concentration, and the assay methods are readily automated. There was reasonably good agreement between the estimated prevalence of ID by the STfR:SF ratio and the previous multiple indicator index in preschool children and women of childbearing age employing samples from the United States NHANES 2003–2006 (32).

Body iron status calculated by using the STfR:SF ratio should, in my opinion, become the standard methodology for surveys of iron status in regions where infectious disorders are uncommon. There is, however, an urgent need for standardization of STfR assays and further research to make affordable reliable assays available worldwide. The best approach in developing countries where malaria is prevalent year round is unclear. Further research to evaluate methods for correcting SF values for the effect of inflammation is needed as well as continued assessment of alternative indicators such as RBC ZPP, CHr, and serum and urine hepcidin concentrations.

There is an urgent need for a clearer understanding of the relationship between anemia and ID in countries where malaria is endemic. It is generally assumed that ID and inflammation are the primary factors responsible for the continued high prevalence of anemia in these regions, each accounting for ~50% (33,34). The Hb response to effective iron interventions in malarious regions is significantly lower than that in other regions (35). It is likely to be a consequence of the persistent effects of malaria and other infections. However, the possible role of α thalassemia carrier status should be reevaluated. Prevalence rates of these polymorphisms are high in regions affected by malaria (36). If thalassemia carrier status modifies the distribution of Hb concentrations by even a small amount, prevalence rates for ID based on Hb alone using WHO cutoff values could be misleading, especially if global estimates are inferred from limited surveys. Although this issue deserves consideration, it should not be overemphasized, because there is persuasive evidence that ID is both common and an important cause of morbidity, particularly among the least privileged children and women of childbearing age in tropical countries.

Consequences of ID

The considerable adverse impact that the high prevalence of ID in developing countries has on people's well-being and productivity receives insufficient recognition from policy makers. Physical work capacity is reduced. ID in pregnancy contributes to the risk of severe anemia and increased maternal morbidity and mortality (37). IDA in early pregnancy is associated with a higher risk of preterm delivery (38). Iron supplementation (usually in combination with folic acid) in pregnancy has been reported to reduce the risk of postpartum hemorrhage (39), improve birth weight (40), and reduce early neonatal (41,42) and childhood mortality (43) in some population groups. Reduced early neonatal mortality was also reported for babies born to women living in malarious regions who received both iron and folic acid supplements and antimalaria prophylaxis (44). Finally, babies born to mothers who did not receive iron supplements in pregnancy were more likely to be iron deficient

TABLE 1 Advantages and limitations of iron status indicators[1]

Indicator	Advantages	Limitations
Bone marrow iron	High specificity	Invasive, expensive
		Technical expertise essential
SF	Quantitative (iron stores), well standardized	Confounded by infection, inflammation (acute phase protein), liver disease
Transferrin saturation	Well established	Wide diurnal variation
		Low specificity
		Not suitable for most field studies
ZPP	Portable assay available[2]	Affected by inflammation, lead exposure
	Result available immediately	Need for improved technology and standardization
	Inexpensive	
	Potential for noninvasive methodology	
STfR	Quantitative (iron deficit)	Affected by erythropoietic rate
	Less affected by infection and inflammation than SF	Standardization incomplete, cost
Hb	Well standardized	Low sensitivity
	Inexpensive	Low specificity
	Universally available	
	Technology suited to field surveys	
RBC indices MCV, MCH, RDW	Well standardized	Low specificity
		Requires automated hematology analyzer
CHr	Early indicator of impaired iron delivery for RBC production	Requires specific automated hematology analyzer
	May be particularly useful in young children (27)	

[1] Adapted from Cook (87).
[2] ZPP:heme ratio, assay specificity is improved by washing RBC to remove plasma interferents (88).

after 4 mo of age in one study from Niger (45). ID in infants and young children is associated with delayed mental, motor, and emotional maturation (46,47). These children may fail to meet educational goals later in life.

The median total annual productivity loss (resulting from the combined effects on physical and cognitive function) in an iron-deficient population has been estimated to be US$16.78/capita or 4.05% of GDP (48). The response to iodine prophylaxis is reduced in goitrous children (49) and the risk of chronic lead poisoning is increased in those exposed to environmental lead (50). Finally, the relationship between iron status and infectious diseases is complex and the subject of considerable debate. However, recent observations indicate that upper respiratory infections are more frequent and last longer in iron-deficient children (51). The risk of severe morbidity related to falciparum malaria is increased (52).

Policy makers have in the past focused on the prevention of anemia. Although this remains a necessary objective, greater efforts should be made to draw their attention to the important functional outcomes described above. They may provide more persuasive arguments, based on more tangible evidence of benefit, for the importance of preventing ID.

Technical and programmatic obstacles

Food fortification. Food fortification is generally considered the most cost-effective method for providing additional iron for populations with a high prevalence of nutritional ID. This approach may, however, not reach people at greatest risk for nutritional ID who depend on subsistence farming and have little access to processed food items. Three categories of fortification are defined in the WHO/FAO Guidelines on Food Fortification with Micronutrients (53). Market-driven fortification of products such as breakfast cereals refers to manufacturer-initiated additions of one or more micronutrients to processed foods, usually with regulatory limits, to increase sales or profitability. It

is common in industrialized societies (54). Targeted fortification is designed to meet the needs of specific groups, e.g. the use of complementary or weaning foods to improve iron nutrition in infants and young children. Mass fortification is defined as the addition of micronutrients to foods such as cereal staples, condiments, and milk commonly consumed by the general population. Many developing countries have introduced regulations to encourage or mandate mass fortification of staple foods. These programs have, however, encountered several obstacles. Technical constraints limit the amount of bioavailable iron that can be incorporated into wheat and maize flour (54). Highly bioavailable iron compounds may affect the storage properties of the flour and change the color and taste of the food (13). Rice is most often eaten as whole grains. Potentially successful fortification methods for rice have been reported only recently (55–57). Fortification, particularly with the more bioavailable forms of iron, increases the cost of production and may not be sustainable, because consumers may not be able to afford even small price increases and government subsidies are difficult to sustain. The staple chosen for fortification may not be consumed in adequate quantities or the iron addition level may be too low. Legislation for fortification may lack specificity allowing manufacturers to be in compliance when adding iron compounds that are less bioavailable. Concerns about the safety of iron fortification, particularly the risk of iron overload among men if mass fortification is introduced, are frequently raised. Wheat and other staples are often imported requiring standardization of fortification regulations between countries and within regions. It is technically difficult to implement flour fortification when milling is carried out in small local mills or at the individual level.

The mass fortification of wheat flour that is being promoted vigorously by the Flour Fortification Initiative (58) illustrates the importance of some of these obstacles. Hurrell et al. (14) recently reviewed current wheat flour fortification practices in

78 countries for which the relevant information was available. They concluded that a positive impact on iron status at the national level would be expected in only 9 countries even if implementation is optimized. In some cases, the average per capita wheat flour consumption or iron addition level is too low. However, the main reason for predicting little effect is the failure to specify a bioavailable iron compound. In 47 countries, the regulations do not stipulate which iron compounds are acceptable for fortification. In most of these programs, millers are likely to use atomized or hydrogen-reduced iron powders because of their low cost and good sensory properties. Reduced iron is actually specified or permitted in 4 countries. Experimental data and human efficacy trials have demonstrated that the bioavailability of these forms of iron is too low to have a significant impact on iron status (59–61).

There are, however, good reasons to be optimistic about the future effectiveness of fortification programs. It is likely that major improvements will occur within the next decade. Innovative approaches to overcoming the technical constraints of providing sufficient quantities of bioavailable iron are gaining support. Ferrous fumarate, a less reactive yet bioavailable form of iron, is recommended or used in many countries in Central and South America (62). NaFeEDTA has been shown to be very efficacious in several field trials (14). The use of encapsulation technologies may provide a practical solution to fortification with more reactive bioavailable compounds (63). Condiments such as salt (64), soy sauce (65), fish sauce (66), and curry (67) may be alternative vehicles for the delivery of fortification iron. Efforts to standardize fortification regulations are being pursued and the necessity for fortifying more than one vehicle in countries with diverse dietary habits has been recognized. However, it will be essential to keep legislators and program managers informed about the necessity of providing iron in a bioavailable form and in sufficient quantities to meet the needs of women, children, and adolescents at highest risk. Finally, Brittenham (68) recently reviewed the safety of flour fortification with iron, concluding that there is little risk of adverse health consequences in developing countries.

Iron supplementation. Supplementation, the provision of iron alone in tablet or liquid form, usually in doses higher than those used for fortification, is customarily recommended in settings where severe ID is detected. The benefits are limited to the period of supplementation and a few months thereafter in individuals whose requirements remain high (69,70). The most appropriate indications are early childhood and pregnancy, because the period of increased requirement is limited. The efficacy of supplementation has been demonstrated in numerous trials, but its effectiveness is questionable, presumably because of poor compliance (71). Furthermore, a trial among young children in Pemba, Tanzania, where malarial transmission is intense and year round, raised questions about the safety of universal iron and folic acid supplementation in regions with high rates of malaria (52).

There have been 2 innovative approaches to improving the effectiveness of fortification in selected at risk groups. The first was the introduction of complementary micronutrient food supplements that can be added to home-prepared weaning foods (72). Three different iron-containing formulations have now been shown to be efficacious in reducing the prevalence of IDA in 6- to 12-mo-old Ghanaian infants (73). The major advantages of this approach are the ability to deliver the iron in a form that can be added to any weaning food immediately before consumption, ease of administration, high bioavailability, and im-

proved compliance. Studies are underway to evaluate its safety in malarious regions. Cost, delivery, and the necessity for the caretaker to be conscientious about regularly adding the supplement to the baby's food remain potential drawbacks. Wider use of this approach to include other family members or the family as a whole is also being explored.

Over a decade ago, Viteri (74) proposed that weekly rather than daily iron consumption could be employed as a more efficient preventive approach to delivering supplemental iron. The efficacy appears to be equivalent to daily dosing in settings other than pregnancy (75). Compliance could be better because of fewer or less frequent side effects. WHO endorses the implementation of weekly iron and folic acid supplementation in women of childbearing age (76). It is a potentially attractive option for women who do not have access to a diet that is adequate in bioavailable iron or to fortified foods, because optimal iron status in early pregnancy appears to be important for preventing prematurity and low birth weight (38,77) and folic acid supplementation during the periconceptual period reduces the risk for the baby of developing a neural tube defect. However, this approach will only be successful if compliance can be sustained over extended periods of time.

Dietary diversification and biofortification. Dietary diversification is the optimal solution to reducing the prevalence of ID. However, obstacles to alleviating poverty and changing people's dietary preferences remain major barriers to this approach. Biofortification (the use of traditional plant breeding methods or genetic engineering to improve the available iron content of staple food crops) holds promise for the future (78). It would make it possible to deliver iron to those most in need. They often depend on subsistence farming and have limited access to fortified foods. A modest improvement in iron stores in nonanemic Filipino women consuming iron biofortified rice was reported in one recent trial (79). However, the meals provided an average of only 1.42 mg/d additional iron. More research is needed to develop successful crops with adequate improvements in bioavailable iron content.

Other issues

A discussion of the failure to reduce the prevalence of anemia worldwide would be incomplete without a brief mention of other conditions that affect iron nutrition. Minimizing iron losses by the implementation of programs to control hookworm infections and schistosomiasis is essential (80). Delayed cord clamping improves infant iron status during the first 4–6 mo of life (81). The possible role of iron malabsorption merits further study. Chronic helicobacter infections are highly prevalent in developing countries and have been reported to be associated with ID because of iron malabsorption and occult blood loss (82). Patients suffering from celiac disease may absorb very little iron. The latter disorder is known to be prevalent in many Western societies and is being recognized more frequently in some developing countries (83). Finally, a hereditary form of iron malabsorption leading to iron-refractory IDA has been recently reported (84). It is an autosomal recessive disorder characterized by IDA unresponsive to oral iron treatment caused by mutations in the gene TMPRSS6, which encodes a transmembrane serine protease (matriptase-2) that is required for appropriate hepcidin regulation. The prevalence of this condition is at the present time unknown as is the possibility that other genetically determined causes of iron malabsorption will be discovered in the future.

In conclusion, there are many reasons to expect that the implementation of strategies for improving iron status that are currently available will substantially reduce the prevalence of nutritional ID in developing countries (85) and be cost effective (86). The impact on the estimated prevalence of anemia, although likely to be significant, is less predictable and may show regional differences.

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