

Safety of Flour Fortification with Iron

Gary M. Brittenham, M.D.
Professor of Pediatrics and Medicine
Columbia University
College of Physicians and Surgeons
Harkness Pavilion, Room HP 568
180 Fort Washington Avenue
New York, New York 10032-3795
Telephone: (212) 305-7005
Facsimile: (212) 305-8408
Email: gmb31@columbia.edu

Introduction

In many developing countries, fortification of flour with iron is now a feasible and cost-effective strategy to reduce the prevalence of iron deficiency¹. In developed countries, fortification of flour with iron during the last half of the twentieth century was an essential factor in the reduction of iron deficiency². Nevertheless, in some of these developed countries, programs of iron fortification of flour have been discontinued, in part because of apprehension about possible adverse effects of iron excess³⁻⁵. We consider here the available evidence about the safety of iron fortification of flour in developing countries.

Background

Remarkable progress has been made over the past decade in understanding the molecular details of iron absorption in humans⁶. Most recently, the long sought intestinal heme transporter has been identified tentatively as heme carrier protein 1 (HCP1), an iron regulated protein localized to the brush-border membrane of duodenal enterocytes⁷. Another signal advance has been elucidation of the means whereby hepcidin, the antimicrobial peptide hormone secreted by the liver in response to iron loading and inflammation, regulates iron efflux from cells which release iron into plasma⁸. In brief, circulating hepcidin binds to ferroportin, the iron exporter on the surface of absorptive enterocytes, macrophages, hepatocytes, and placental cells, causing internalization and degradation of the complex. Removal of ferroportin from the cell surface results in cellular retention of iron. This hepcidin-ferroportin interaction is likely to be central to understanding the pathogenesis of iron overload; most forms of inherited iron overload are associated with hepcidin deficiency⁹, or, more rarely, with autosomal dominant mutations of ferroportin¹⁰. Moreover, a delay in hepcidin response – rather than “programming” and migration of enterocytes from intestinal crypts to the villus tip – seems to be responsible for the lag period between certain stimuli and a subsequent change in intestinal iron absorption¹¹.

Tolerable upper limits for daily intake of dietary iron

Assessment of the safety of iron fortification of flour must take into account the amount of iron that will be provided. The tolerable upper intake level of a micronutrient is the maximum level of total chronic daily intake of the nutrient from all sources that is judged to be unlikely to pose a risk of adverse health effects to humans¹². Conceptually, the maximum amount of a micronutrient that can be added to the diet with little risk of adverse effects can be estimated as

the difference between the tolerable upper limit for daily intake and the current intake¹². Determining these levels for iron has been difficult, in part because absorption of heme iron is much higher than that of non-heme iron and the bioavailability of non-heme iron varies by more than an order of magnitude¹³. In addition, uncertainty remains about the ability of healthy individuals to maintain normal levels of body iron with an iron-rich diet or with chronic administration of supplemental iron. Overall, some authorities judge that “ingenious systems available in the body for controlling iron absorption and the internal distribution of absorbed iron will prevent the development of dietary iron overload in otherwise healthy subjects”¹⁴. Other investigators express concern that “down-regulation [of iron absorption] at high intake levels seems insufficient to prevent accumulation of high iron stores at high intake”¹⁵. With decisive evidence lacking on the possible role of iron in the pathogenesis of cardiovascular and other disorders, the Panel on Micronutrients of the US Food and Nutrition Board developed their estimate of the tolerable upper intake level for dietary iron (45 mg/d) on the basis of the gastrointestinal side effects of pharmaceutical iron preparations¹⁶. This choice has been criticized and an alternative proposed that would recommend a dietary iron intake that meets dietary iron requirements but does not substantially exceed them¹⁷. The European Commission Scientific Committee on Food has not yet established a tolerable upper limit for dietary iron but other national and expert groups have suggest various values¹². Overall, no global consensus on a tolerable upper limit for daily intake of dietary iron has been reached. Nevertheless, in developing countries the amounts of iron added to the diet by flour fortification programs have difficulty in supplying amounts adequate to meet dietary iron requirements and would generally have little risk of exceeding even the most conservative estimates of tolerable upper limits.

Potential hazards of flour fortification with iron

Consideration of the safety of flour fortification with iron will be restricted to potential hazards in populations in developing countries with diets including little heme iron from meat sources and with non-heme iron of limited bioavailability. A number of more general reviews are available with discussions of possible risks in developed countries with diets containing a variety of iron-rich foods^{2, 4, 5, 14, 15, 18-25}.

Interactions with other nutrients: Ferrous iron (Fe^{2+}) enters the absorptive enterocyte through the divalent metal transporter 1 (DMT1; also identified as DCT1 or Nramp2). DMT1 has a broad substrate range that also includes Zn^{2+} , Mn^{2+} and Cu^{2+} ^{6, 26}. As a consequence, the addition of fortification iron could potentially interfere with the absorption of other divalent ions. While larger doses of supplemental iron may inhibit zinc absorption^{27, 28}, the effect is diminished or absent when given with food²⁹⁻³¹. Studies using radioisotopic labeling of single meals found that the addition of iron to food at fortification levels did not impair absorption of zinc²⁹. Similarly, iron fortification of food seems to have little or no effect on the absorption of manganese³¹⁻³³. Mechanisms of copper absorption are incompletely characterized³⁴ but seem to involve the copper transporter hCtr1^{35, 36} as well as DMT1. In human studies, iron supplements did not inhibit intestinal copper absorption³⁷, suggesting that iron fortification of flour is unlikely to interfere with copper absorption. Overall, with the amounts of iron used for flour fortification, none of the available evidence suggests a meaningful risk of interference with the absorption of other divalent ions.

Iron overload: Iron overload is the general term used to describe an excess in total body iron. Humans are unique in lacking any effective means to excrete excess iron. As a consequence, the amount of iron within the body is physiologically controlled by meticulous control of iron absorption. Iron stores and absorption are reciprocally related, so that as stores increase, absorption decreases. Iron overload develops in conditions that alter or bypass the normal control of body iron content by regulation of intestinal iron absorption. Globally, both

genetic and environmental factors determine the types and prevalences of iron overload. In populations of northern European ancestry, a genetic disorder, the homozygous state for hereditary (*HFE*-associated) hemochromatosis, is the most common type of iron overload¹⁰. Autosomal dominant hemochromatosis due to ferroportin mutations has been reported from a variety of ethnic groups but comprehensive data on its global distribution and prevalence are not yet available. Apart from hereditary (*HFE*-associated) and autosomal dominant hemochromatosis, other types of primary iron overload seem to be uncommon or rare disorders. In an area bordering the Mediterranean and stretching from Southwest Asia and the Indian subcontinent to Southeast Asia, the most common types of iron overload are those associated with the iron-loading anemias and transfusion-dependent disorders such as the thalassemias and related hemoglobinopathies³⁸. In sub-Saharan Africa, dietary iron overload associated with consumption of iron-rich brewed beverages is a common problem which likely also has a genetic component^{39, 40}. In addition, iron overload develops in patients with iron-loading anemias or in chronically transfused disorders, including sideroblastic and myelodysplastic anemias, thalassemia major and intermedia, congenital and acquired refractory anemia, and sickle cell anemia when red blood cell transfusion is used for prevention of stroke or other complications.

Risks of iron fortification in individuals with normal regulation of iron absorption:

As noted above, the effect of orally administered iron on body iron stores in individuals with normal control of iron absorption is uncertain and few data are available. Case reports have documented iron accumulation in patients who have taken medicinal iron for extended periods⁴¹, but the possible role of an unrecognized genetic abnormality associated with iron loading in these individuals cannot be excluded. In one study of iron fortification, increase of iron intake by 7.5 mg per day produced no increase in estimated iron stores of iron-replete men compared with controls⁴². In one iron-replete man, dietary iron supplementation for 500 days did not change the serum ferritin concentration⁴³. Overall, especially in populations in developing countries, the amounts of iron supplied by flour fortification would seem to pose no significant risk of causing iron excess in individuals with normal regulation of iron absorption.

Risks of iron fortification in individuals with impaired regulation of iron absorption: By contrast, in individuals with hereditary or acquired disorders affecting control of iron absorption, iron fortification will contribute to iron loading but the additional increment in body iron burden in most individuals would be minor. The recognition that most forms of dietary iron loading are associated with hepcidin deficiency provides a means of estimating the rates and risks of iron loading. Juvenile hemochromatosis is a rare form of iron overload with complete absence of hepcidin synthesis, occurring in individuals homozygous for mutations in *HAMP*, the gene for hepcidin⁴⁴ or, more often, for mutations in the gene for hemojuvelin⁴⁵, now known as *HJV*. In patients with severe juvenile hemochromatosis, regulatory hepcidin control over absorption of iron seems to be completely absent⁴⁴. In these individuals, so far identified only in developed countries with iron-rich diets, the accumulation of a clinically evident toxic load of iron requires 20 to 30 years. For comparison, individuals homozygous for hereditary (*HFE*-associated) hemochromatosis produce hepcidin but seem unable to increase expression appropriately as body iron stores enlarge⁴⁶. Even in developed countries with iron-rich diets, the penetrance of *HFE*-associated hemochromatosis seems low^{47, 48}, and clinical expression of iron overload is typically delayed until the fourth or fifth decade of life, or later. The rates of iron-loading in most other forms of iron overload seem to lie between those in juvenile and hereditary hemochromatosis. In these individuals, the added increment of iron that would be derived from fortification would be unlikely to increase dietary iron to levels found in developed countries. Consequently, flour fortification would be expected to increase the rates of iron loading by only a very limited extent. Moreover, in most developing countries, *HFE*-associated and other

genetically determined forms of hemochromatosis are uncommon or rare disorders. Instead, the greatest risk of iron loading is in patients with iron-loading anemias or chronically transfused disorders, including thalassemia major and intermedia. In transfused patients, the amounts of iron derived from red cells dwarf dietary iron absorption and iron-chelating therapy provides a means for effective treatment of both. In patients with iron-loading anemia, especially thalassemia intermedia or the Hb E/ α -thalassemia syndromes, iron fortification will increase the rates of iron loading but, as in patients with primary iron overload syndromes, only by a very limited extent. The uncommon and rare individuals with these iron-loading conditions are best managed by screening and treatment of affected individuals rather than by withholding of iron fortification from the large population that would benefit.

Adverse effects involving immunity and infection: The interrelationships between iron, immunity and susceptibility to infection are multifaceted, complex and still incompletely understood. With this caution, most concerns about adverse effects of iron have been raised by studies in which iron was given parenterally or as an oral supplement rather than as a fortificant. The available data from areas with and without endemic malaria may be considered separately.

Areas without malaria: In brief, in non-malarial areas, a comprehensive review of published studies found no evidence that iron fortification increases infectious morbidity⁴⁹.

Areas with malaria: Interpretation of the results of studies of the effects of iron on malaria require an appreciation of differences in the endemicity of malarial infection in different regions. The clinical presentation of falciparum malaria, the form responsible for most morbidity and mortality worldwide, depends upon the intensity of malaria transmission. Where transmission of *P. falciparum* is both stable and intense, as in much of sub-Saharan Africa, symptomatic malaria is primarily a disease of young, non-immune children with chronic malarial infection. Repeated episodes of malarial infection in childhood eventually result in resistance to the clinical effects of malaria. Older children, adolescents and adults are asymptomatic by virtue of acquired immunity but most or all of the population has persistent parasitemia. In regions with lower frequencies of malarial transmission, immunity declines and older individuals may develop symptomatic and severe disease. In areas of low malaria transmission, as in most of southeast Asia, acquired immunity is still less protective, asymptomatic parasitemia is unusual, and acute malaria may occur at any age. In 1999, a consensus statement by the International Nutritional Anemia Consultative Group (INACG) of the safety of iron supplementation in malarial areas, based on a meta-analysis of 13 controlled, randomized trials, concluded that “clinically important risk elevations are not ruled out by these data, but the evidence for them is weak”⁵⁰. A subsequent review found that evidence for a dose-related, immune-mediated effect of iron on increasing the risk of clinical malaria have been restricted to oral iron supplementation of children at doses greater >2 mg iron/kg/day living in tropical areas with intense transmission⁴⁹. Because iron fortification of flour would provide amounts of iron well below this level, the risk of adverse effects with respect to malarial infection seem remote. In addition, since the INACG consensus statement, four prospective, randomized and controlled studies have found no evidence of adverse effects of iron⁵¹⁻⁵⁴.

Cardiovascular disease, diabetes and cancer: The suggestions that a high dietary intake could increase the risk of cardiovascular disease, type 2 diabetes and cancer has lead to a number of studies and reviews examining these possibilities^{15, 19-21, 24, 25, 55, 56} but virtually all are relevant only to developed countries with iron-rich diets. Even in these circumstances, no definitive evidence of a relationship between iron intake and cardiovascular disease or type 2 diabetes has been developed. Concerns about colorectal cancer relate to high iron intakes in iron-replete individuals²¹. Overall, in populations in developing countries, the risks of iron fortification of flour contributing to development of cardiovascular disease, diabetes or cancer seem increasingly small.

Priorities for future investigation:

Carefully designed programs for epidemiologic surveillance to detect the adverse effects of iron fortification considered above should be developed and integrated into plans for monitoring populations after the introduction of iron fortification of flour.

Further investigation is needed to fully define the risks and potential consequences of the interaction of iron fortification of flour with other micronutrients, especially in circumstances where only iron is the single added nutrient. In particular, the effect of flour fortification with iron on measures of zinc and copper status should be included in programs monitoring the effects of fortification.

Additional study is needed to clarify the effects of iron fortification of flour on the prevalence of malarial infection in different geographic regions of the world with different intensities of malarial transmission.

Conclusion

Fortification of flour with iron to reduce the prevalence of iron deficiency in developing countries carries remarkably little risk of adverse health effects.

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