Review Article

A Comparative Review on Iron Deficiency Anemia among Children and Long-Term Strategy

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Abstract

Background:One of the most prevalent dietary disorders in the world is iron deficiency anemia (IDA) which impacts people of all ages, genders, and physiological categories. In the current situation, iron fortification in food is seen as a long-term, cost-effective, and sustainable technique. ***Scope and approach:*** The ideal mix of iron form and food carrier, as wellas the food circumstances in which it is consumed, are critical.Combining iron with a bioavailability booster and avoiding interactions with iron inhibitors are suggested. As a result, this paper provides a thorough examination of the high prevalence of IDA, its various causes, absorption of haem and non-haem iron, and bioavailability,in addition to iron fortification strategies. ***Results:*** Ascorbic acid and meat components in animal tissue are the most prominent enhancers of iron absorption in diets. Polyphenols, phytates, and calcium are the utmost potentinhibitors of iron absorption. Additional approaches to minimize iron uptake from diets may include changes in diet that lower iron consumption and reduce iron bioavailability. ***Conclusion****:* Food fortification is a viable technique for lowering anemia prevalence. The combination of iron fortificants and food vehicles should be harmless, agreeable, and ingested by the target population for an effective fortification program.It should also have no negative impact on the ultimate product's acceptance and stability. Novel food fortification techniques may lead to the development of new approaches to treating iron deficiency and anemia.

Keywords: Iron deficiency anemia, children, bioavailability, iron fortification

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Introduction

The utmostcommunal nutritional problem in the world is iron deficiency anemia. The incidence varies across the globe, with greater rates in developing nations.[1] Anemia affects above 30% of the global population.[2]Except for China, where the frequency of IDA is lower, IDA is also an issue across Latin America, the Middle East, the Caribbean, East Asia, and the Pacific, where the prevalence of IDA ranges from 22 to 66 %.[3] Anemia continues to be a major global health issue, impacting 43% of children underthe age of five, 38% of pregnant women, and 29% of non-pregnant women globally.[4]Southern Asian and African childrenare especially vulnerable, with IDA affecting more than 50% of children of preschool age in most nations.[4]

Anemia is a condition in which there isn't enough iron in the body to maintain normal red cell production.[5] It develops when the body's

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physiologic requirements for red blood cells (andas a result, theircarrying capacity for oxygen) are not met. Globally, Iron Deficiency is thought to be the most significant reason for anemia.[6] When bodily stocks of iron are depleted, such as when there is an increased need for iron or when iron intake and absorption are reduced, iron deficiency (ID) occurs.[7]

ID mainly affects newborns and young children in most parts of the world, due to their greater iron requirements associated withgrowth, and females of the childbearing stage, as a result of menstruation loss and pregnancy.[8,9] Young kids are particularly susceptible to the effects of IDA since their body systems are working to develop, particularly their brains, which are the quickest developing organs during infancy and early childhood.[2] It can cause major public health problems, such as increased disease and mortality in children, as well as impaired growth, immune system, and cognitive development, decreased physical activity, low endurance capacity, and poor learning ability.[2,10,11]

Anemia is caused by a variety of factors in developing countries, including nutritional deficiencies (iron, folate, and vitamin B12), infectious disease, for example,malaria and intestinal parasite infection, and chronic disease.[5] Iron deficiency anemia arisesresulting from a shortage of iron-rich meals and the availability of iron absorption barriers in the diet.[12] Childhood anemia is a multi-factorial environmental condition.Poverty, ignorance, improper cooking, a shattered family structure, reducedconsumption and storage patterns, and, of course, a lack of educational knowledge all have various impacts on childhood anemia.[13] Mother's anemia during pregnancy, and a lack of breastfeeding also contribute to an increased occurrence of the disease in children.[14]

In this context, communityhealth measures to prevent and control anemia include a variety of iron-supply alternatives now available, although iron dietary fortification appears to offer the greatest risk-benefit ratio.[15] In the long run, this remains anauspicious and moneymaking method of focusing on a certain set of people. Since they have an impact on nutrient bioavailability, the chosen food carrier, and the aimed micronutrient must be synergistic. Therefore, understanding the destiny of iron and its bioavailability is critical for the creation of plannedmethodologies to alleviate anemia through iron supplementation.

Prevalence of IDA

Iron deficiency is the most common and widespread nutritional disorder in the world, impacting a lot of children in developing countries as well as many in developed countries. The prevalence of IDA is depicted in Table 1.

Table 1. Nutritional disorder in selected countries in the world

Year	Country	Age	Prevalence of Anemia (%)	Prevalence of IDA (%)	Reference
2020	Indonesia	5 -14 years	26.4	5.8	Andriastuti et al., 2020[16]
	Libya	<5 years	50.4	49.5	El-mansoury, 2020[10]
	Brazil	<59 months	20.9	-	
	Ethiopia	6-59 months	44	-	Central Statistical Agency Ethiopia & MEASURE DHS - ICF Macro, 2011[17]
	Bangladesh	6-23 months 24-59 months	-	64 42	Rashid et al., 2010[18]
	Angola	6-23 months	52	23.92	Fançony et al., 2020[19]
	Myanmar	6 – 36 months	-	72.6	Zhao et al., 2012[20]
	Malaysia	1-6 years 7-12 years	36.7 25.6	26.7 16.3	Ngui et al., 2012[21]

Determinants of IDA

ID is multifactorial in the world, and IDA arises from a bigger framework of biological, cultural, and socioeconomic factors, with both direct and indirect causes and components.

Table 2. Determinants of iron deficiency anemia

Factors	Iron Deficiency Anemia (%) in different countries							
	Kenya	Sri Lanka	Angola	Lebanon	Brazil	India	Ethiopia	Japan
Age								
< 6 months		33	16.4	25				
6 – 8 months	76.5	83			39.9	75.3	43.8	
9 – 11 months	64.8		54.9			78.9		
12 -23 months	68.9	72		71.4		78.7		57.8
24- 35 months	-	40	28.8			68.2	56.2	37.4
36-47 months	-					58.2		34.6
48 – 59 months	-		-		26	48.3		29.2
Sex								
Male	75.5	53	51.6	38.9	41.7	64.6	48	44.9
Female	74.4	51	41.4	34.8	27.7	64.9	52	41.0
Mother's educational level								
None	-	-	-	-	-	71.7	22.7	47.2
Primary	25.6	59	36.3	39	-	65.9	54.4	42.2
Secondary	74.4	42	50.4	23.1	-	59.6	23	45.1
Higher	-	-	13.3	-	-	49.7	-	44.4
Income per month								
Low	34.4	-	59.1	43.5	-	67.8	59.2	-
Medium	25.1	-	40.9	31.5	-	67.3	35.3	-
High	30.8	-	-		-	58.3	5.4	-
Wealth index								
Poor	-	-	-	-	-	75.6	38.1	41.8
Middle	-	-	-	-	-	65.2	24.8	44
Rich	-	-	-	-	-	52.7	37.2	42.7
Residence area								
Urban	-	-	-	33.3	-	67.4	-	42.5
Rural	-	-	-	39.3	-	60	-	44.0
Size of family								
< 5	-	-	35.3	-	-	-	67.1	45.2
>5	-	-	27.6	-	-	-	32.9	43.4

Factors	Iron Deficiency Anemia (%) in different countries							
	Kenya	Sri Lanka	Angola	Lebanon	Brazil	India	Ethiopia	Japan
Duration of breast feeding								
<180days	-	-	49.3	-	28.2	-	-	-
180 – 360 days	-	-	52.5	-	41.9	-	-	-
>360 days	-	-		-	35.8	-	-	-
Treated drinking water (boiled for children)								
Yes	-	58	73.5	-	-	-	-	42.7
No	-	50	49.6	-	-	-	-	44.7
Consumption of meat and fish								
Yes (non- heme)	-	-	35.3	-	32.4	-	18.7	-
No (heme)	-	-	75.8	-	70	-	68.6	-
Consumption of fruits (previous day)								
Yes	-	60	-	-	-	-	-	-
No	-	48	-	-	-	-	-	-
Consumption of dark leafy vegetables								
Yes	-	-	-	-	30.7	-	14.8	-
No	-	-	-	-	43.1	-	30.5	-
Cow milk intake								
Yes	-	-	-	42.9	-	-	-	-
No	-	-	-	-	-	-	-	-
References	Wangusi et al., 2016[22]	Malkanthi et al., 2010[8]	Fançony et al., 2020[19]	Mhanna et al., 2016[23]	Nambiema et al., 2019[24]	Bharati et al., 2015[25]	Orsango et al., 2021[26]	Keokenchanh et al., 2021[27]

Dietary Iron Absorption

1. Iron absorption:

Food contains two types of iron: non-haem iron and haem iron. Non-haem iron is found in both plant and animal's foods, whereas haem iron is only derived from animal products.Although iron is absorbed mostly in the duodenum, the methods of absorption for these types differ.Iron absorption across the enterocyte is commonly regarded in terms of three processes. They are iron utilization from the food across the brushborder and then into the enterocyte, an intracellular process in which iron is aimed directly to the basolateral membrane for delivery to the circulation, storage, or utilization within the enterocyte, and iron transfer across the basolateral membrane, also known as the transfer step. Non-haem iron invegetables and grains is absorbed more slowly than dietary haem iron. The proximal intestine absorbs the majority of haem, with absorption capacity diminishing as you move farther away. HCP1 (haem carrier protein 1), an intestinal haem transporter, has been recognized and found to be significantly expressed in the duodenum. Hypoxia and iron shortage enhance its activity. BCRP (breast cancer resistant protein) and FLVCR are two exporter proteins (feline leukaemia virus subtype C),that allow some haem iron to be reabsorbed intact into the cell's circulation. The duodenum would be the primary site for non-haem iron absorption. A brush border ferrireductase converts non-haem iron from ferric to ferrous form and the low pH of the stomach dissolves non-haem iron. Cells in the duodenal crypts can recognize the iron requirements of the body and store this data as they develop into the cell's capacity to absorb iron at the villi's tips. Iron is transported across the apical (luminal) exterior of small intestinal mucosal cells by the protein called divalent metal transporter 1 (DMT1) or natural resistance-associated macrophage protein (NRAMP2).Irons are carried crosswiseto the apical (luminal) surface of the mucosal cells in the small intestine by a protein called divalent metal transporter 1 (DMT1) or natural resistance-associated macrophage protein (NRAMP2). Iron might be transported through the cell to enter the plasma or kept as ferritin once within the mucosal cell;the iron condition of the body system at the time the crypt cell originates adsorbing cell is certainly the determining factor. When mucosal cells are shed, Iron is misplaced in the intestinal lumen after being stored as ferritin., regulating iron equilibrium. Theirontransportationthrough the basolateral surface of mucosal cells is regulated by ferroportin 1 (FPN 1), a transporter protein including an iron-responsive element (IRE). Hephaestin, a multicopper protein, is needed by this transporter protein.Iron absorptionregulates the body's iron level, however there is no physiological process for removing unnecessary iron. The main molecule that controls iron absorption is hepcidin, a 25-amino-acid peptide produced in the liver. Hepcidin regulates the function of the iron-transferring protein ferroportin by binding to it and causing it to be internalized and destroyed, resulting in a reduction in iron efflux from iron-exporting tissue into plasma. As a result, inflammatory cytokines such as IL-6, which produce high levels of hepcidin (which occurs in inflammatory situations), degrade ferroportin and impede iron absorption.[28]

2. Nutritional enhancers

a) Ascorbic acid (AA)

Adding enhancers of iron absorption to fortified foods mightprogress the efficacy of fortification schemes, particularly in foods containing inhibitors including phytate and tannins.[29] The most efficient booster of iron absorption is vitamin C. With a molecular weight of 176.13 and the empirical formula $C_6H_8O_6$, it is a chemically defined compound.[30] Vitamin C helps convert Fe3+ (ferric) iron to Fe2+ (ferrous) iron, which is the most easily absorbed form. Vegetarians frequently consume a significant amount of vitamin C, which is found in a variety of fruits and vegetables.[31]Adding vitamin C to a test food with a molarity of 1.6:1augmented iron absorption considerably[32], whereas adding vitamin C to a test food with a molarity of 4:1 augmented non-heme iron intake by 185 percent.[33]The beneficial effect of AA on iron absorption from a complete diet is less pronounced than in single-test-diet studies.[29] In the overall diet research, however, The consumption of ascorbic acid is related to iron absorption.[29]Between 2010 and 2014, The European Food Safety Authority investigated the relationship between ascorbic acid and iron absorption and concluded that "vitamin C contributed significantly to increaseabsorption of non-heme iron.[34] According to research, vitamin C from maize and wheat improved iron absorption in these cereals by up to 84 percent and 48 percent, respectively.[35]It should be remembered that Temperature and air exposure are both important factors for AA. and that oxidation to dehydroascorbic acid during preparing food can diminish AA content.[30] Several ascorbic acid compounds are less heat and oxygen susceptible. A study recently presented that after being baked into iron-fortified bread, ascorbyl palmitate conserves its boosting result on the absorption of iron.[30,36]

b) Animal tissue

Muscle tissue, whether it's from meat, fish, or chicken, enhances non-heme iron absorption, particularly in cereal and legume-based diets. Meat enhances iron absorption in a variety of ways, involving chelation and stomach acidity impacts. Initially, by boosting gastric acid production and, as a result, improving iron solubilization in the stomach. After that, in the stomach's acidic (lower pH) environment, a meat component may chelate the solubilized iron, retaining iron solubility during intestinal digestion and absorption. Absorption of non-heme iron was increased 2–3-fold when chicken, beef, or fisheries were added to a maize meal, comparedto no effect when the same quantity of protein was delivered as ovalbumin.[37] In young women, incorporating pork meat (50 g or 75 g) into food with 220 mg of phytate and 7.4 mg of vitamin c, which was thought to have low iron bioavailability, dramatically enhanced iron absorption.[38] When salmon fish was added to a high-phytate meal, it was found that such sum of salmon consumed could significantly increase iron absorption from bean meal.[39] The enhancing impact of animal tissue is unaffected by cooking temperature.[40] However, by converting haem iron to non-haem iron,41 reduces the amount of haem iron in the body, potentially counteracting iron absorption.

3. Inhibitors

a) Phytate

Phytate (myo-inositol phosphate),themajor blocker of absorption of non-haemiron is a biologically active molecule abundant in plant-based foods.[42] Legumes, nuts, whole grain cereals, and unprocessed bran are examples. Dependent on the numberof phosphates related to the inositol ring, inhibit the absorption of non-haem iron. The most powerful iron inhibitors are inositol hexaphosphate and inositol pentaphosphate, which have a dose-dependent impact.[43] Highermolarratios of phytate: iron (>1) diminish iron absorption.[39] The usage of marketable phytases for phytate dephosphorylation has been stimulatedsubsequently the collaboration is due to the complexion of positively charged metal iron with phytate's negatively charged phosphate groups.[44]Long-term regular consumption of wheat bread containing a high proportion of whole-grain reduced the body's natural iron levels (serum ferritin)among vegetarians[45] and in young women.[46]Lactic acid fermentation reduces the phytate concentration of cereal flours[47] more effectively than yeast fermentation.[48]

b) Polyphenols

Polyphenols are a heterogeneous set of complexes present in fruits, berries, vegetables, spices, pulses, and whole grains, with a high concentration in tea, coffee, chocolate, red wine, and some herbal teas.[49]The phenolic combinations from the meal or drink are released during digestion and could form a bond with Fe in the intestinal lumen, rendering it inaccessible for absorption.[50]According to a study, Beverages usually contains 20–50 mg of total polyphenolic compounds per serving reduced iron absorption from a bread diet by 50–70%, while beverages possessing 100–400 mg of total polyphenolic compounds per serving reduced uptake by 60–90%.[51]When compared to water as a control drink, tea restricts non-heme iron absorption by at least 37%, according to research. It also found that a one-hour time delay between tea drinking and a meal neutralizes these inhibitory activities by at least 1.6-fold. Black tea is a good example of an iron inhibitor, as are green tea, coffee, chocolate, wine, herbs and spices, and seeds to a lesser extent. The percentage of people affected by black tea ranged from 79 to 94 percent.[52,53]Iron absorption was reduced by 59 percent ($P < 0.001$) and 49 percent ($P < 0.05$) in iron deficiency anemia and control personscorrespondingly, when a cup of tea drink was added to the reference meal.[54]

c) Calcium

Calcium is also thought to limit the absorption of iron, respectively haem and non-haem. However,a new study reveals that calcium has only a minor impact on the absorption of iron over time (potentially as a result of a physiological adaptation).[55] Bovine milk and milk-based products seem to be the most calcium-rich foods. Spinach, broccoli, cabbage, and okra are examples of green vegetables,[56]as well as some legumes like soya beans, which contain significant levels of calcium. In single-test-meal research, dairy items and calcium complement reduced iron uptake;the effect was contingent upon thesimultaneous accessibility of iron and calcium inside the colon, and it was also demonstrated when calcium and iron were provided together while fasting.[29]Dose-dependent inhibiting results were noted when calcium was delivered to bread rolls at dosages of 75–300 mg and calcium via dairy items at levels of 165 mg.Calcium appears to have a negative impact on the absorption of iron in single-diet studies, so although calcium appears to have only a minor impact on iron absorption in numerous-food researches that used a variety of ingredients and varying amounts of other inhibitors and stimulants.[43] However, it's probably better to evade taking high calcium supplements with food.

Iron fortification

The most cost-effective and long-term plan is to lower the occurrence of IDis to fortify foods with iron.It's a well-received public-health initiative. The purposeful increased amount of a vital trace element within diet is known as fortification, including minerals and vitamins (includingtrace elements), to improve the nutrient quality of the food supply while posing minimal health risks.[57]The effectiveness of iron fortification in enhancing iron status is dependent on a number of parameters, including the vehicle chosen,the iron complicatesutilized, as well as the iron level of the population under consideration.The selection of food that will serve as a carrier for the trace elementis the most important step in a fortification program and must be a regular part of the overall population's diet, should be inexpensive to the target group, consumed on a regular basis, and available in predictable quantities.[58] Solubility is a key characteristic of fortificants, and it has been classified into three types: i) dissolvable in water, ii) dissolves in dilute acids but weakly soluble in water, and iii) insoluble in water but, it is low soluble in dilute acids.

i) Iron compounds that are water soluble.

Ferrous sulfate is generally the first choice for iron fortification due to its excellent relative bioavailability and low cost. However,its major drawback isthat it is highly unstable and that its oxidation is temperature and air-exposure reliant., and that it might cause undesirable sensory attributes changes.[59] The adding of ferrous sulfate to various cereal flours, particularly those kept in warm, moist environments, could cause lipid rancidity.[60]

ii) Poorly Water-soluble compounds with well soluble in gastric juice.

Although ferrous fumarate seems to have the same bioactivity and solubility as ferrous sulfate, it has a far lower organoleptic impact. It's commonly used to boost the nutritional value of cereal-based supplemental foods.[60]

iii) Water-insoluble and low solubility in dilute acids

The chosen iron compounds for diets are ferric orthophosphate and ferric pyrophosphate (FPP), which are primarily utilized in the fortification of various infant cereals, rice, and chocolate-contained food.[61]They have reduced bio accessibility compared to the others, which is a vital factor for bioavailability[60], but they are also more susceptible to undesirable color and flavor alterations, as these molecules tempt minimal if any sensory changes.

It is essential to choose the optimum blend of fortificant and vehicle when designing iron-fortified food,considering the people who will gain from its consumption. Powder infant formulae are an excellent example of this approach. They usually have ferrous sulfate, which is 100 percent soluble when re-formed, and ascorbic acid, which ensures adequate iron bioavailability.[62]Cereal meals, whether for weaning or adulthood, are attractive contenders for fortification since they are the maindiets in many cultures everywhere in the entire globe andit could be processed into a solid form that makes iron-fortified grain foods.ferric pyrophosphate,electrolytic iron Ferrous sulfate, and ferrous fumarate are the iron complexes suggested by the WHO for the fortification of cereals.[63]Seasonings including fish sauce, soy sauce, table salt,and curry powder were tested as food carriers with iron supplements, in addition to infant formula and main meals, due to their widespread usage in severalaim groups.[64]

Iron bioavailability

While iron insufficiency remains one of the most prevalent dietary problems globally, justifying long-lasting worldwide attempts to rise iron consumption in high-risk populations, little nutritional bioavailability of iron remains the primary cause of anemia in both industrialized and developing countries.[65]Iron bioavailability refers to the percentage of iron consumed which is digested by the intestine and used throughout regular metabolic processes or retained.[59]Even when an acceptable amount of nutritional/ supplemental iron is supplied, normal persons are predicted to have a wide range of iron absorption efficiency.[66]The inverse link between absorption of iron and the size of bodily iron status, as well as the kinds of food, mixtures of foods, and timing of food intake, all influence the mineral's maximum removal capability from the meal.[67] Although ferrous iron is thought to be better absorbed than ferric iron, both ions could be effectively absorbed as long asthey are soluble when they approach the mucosa. Because ferric salts could precipitate as P^H increases from the stomach to the duodenum, solubility is the limiting factor.The precipitation of iron can be avoided by combining it with chemicals that create absorbable chelates that stay soluble when the non P^H rises.[59] In general, haem iron is absorbed more quickly (15–40%) than -haem iron (1–15%). Pigs were utilized in a study to see how the bioavailability of four different iron compounds affected the fortification of cereals. The inquiry makes use of micronized dispersible ferric pyrophosphate (MDFP), ferrous fumarate (FF), electrolytic iron (EI), and ferrous sulphate heptahydrate (FSH).The data show that EI is less effective in replacing stored iron than other compounds. Because the iron bioavailability of FF and MDFP was equal, the iron reserves of the weaned piglets increased significantly. As a result, dietary patterns have a massive influence on dietary iron distribution and absorption.[68]As a result, a well-balanced combination of foods can aid in boosting iron status and bioavailability.

Viewpoint on the future

The results suggest that more research into many aspects of IDA in children and other demographic groups is recommended. The issue of anemia should be examined from a regional standpoint. This has the potential to result in enormous national and international transformations. The problem could be better addressed by identifying region-specific diets that could serve as potential food vehicles, conducting studiesand developing maintainable food fortification methods, developing innovative food formulations that take into account enhancers and inhibitors of iron absorption, and, most significantly, raising public awareness about the importance of healthy diets and food micronutrients.Iron fortification studies must take into account the cost-benefit ratio because it is an issue of worldwide interest. The barriers to implementing the boosting measures, on the other hand, must be removed. Additionally, the price of some fortification methods might put the cost of food out of reach for people who require the most nutrients. This constraint could be overcome by employing less expensive alternatives, such as food-to-food fortification using local resources. Nevertheless, there is a lack of understanding of the procedures and benefits of food-to-food fortification.

Conclusion

As iron deficiency seems to be the most common dietary deficiency, there is clearly a social necessity, andthe number of consumers is huge. In this framework, precision nutrition-based advice developed for specific populations isbecoming more common. As a result, fortification remains the harmless way to report the problem of iron deficiency. Iron fortification would be more in line with the human body's functioning and physiology.It's critical to understand the major components of iron-fortified foods. Relationships between iron supplement, a food carrier, and customer demand for a multi-disciplinary strategy method. It's also worth noting that the solubility of iron complexes in the gastrointestinal tract influences the relationship between the absorption of iron and iron status. There is a need for a better knowledge of nutrient bioavailability as well as solutions to the fortificant's sensory attributes and degrading issues. Most attempts to prevent iron deficiency through fortification schemes have focused on overcoming technical issues such as discoloration, off-flavor formation, and fatty acid oxidation, often ignoring other practical issues that are critical for effective implementation.The involvement of iron fortification in bioavailability causes is hard to assess because the intake of iron-fortified food products and the bioavailability of iron-fortification constituents differ greatly.

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