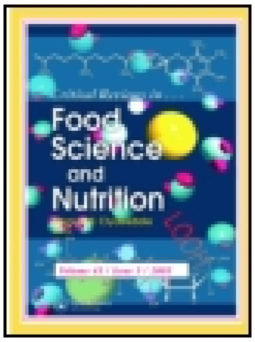

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REVIEW

An overview on mechanism, cause, prevention and multi-nation policy level interventions of dietary iron deficiency

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ABSTRACT

Iron deficiency anemia (IDA) is probably the most ignored situation in the world of malnutrition—largely due to its slow progression. Multiple reasons can be attributed as the cause of IDA, which is not limited to any specific region or population; therefore, making it a matter of global concern. Despite the human body's ability to absorb and conserve iron stores, the gradual loss due to various physiological conditions leads to net deficiency of iron. Countless commercial iron supplements are available, but at given physiological conditions, almost all of these "Bio-not-available" iron forms quite often become ineffective. World Health Organization and other government bodies have jointly developed health advisories and tried to developed nutrition supplements several times in the last two decades. IDA, when combined with other disease conditions, becomes a life-threatening situation. At the same time, an overdose of iron could also be very harmful to the body. Therefore, it is important to deal with this situation with caution. This article covers iron metabolism, available options for iron supplementation, regulatory aspects and strategies to prevent IDA.

KEYWORDS
Bio-available iron; dietary iron fortification; global policy intervention; iron deficiency anemia; iron metabolism

Introduction

Despite being the second most abundant metal in the earth's crust, iron deficiency is the world's most common nutritional disorder leading to iron deficiency anemia (IDA). Broadly, criteria to identify IDA consist either of a low hemoglobin (<7.7 mmol/l in men and 7.4 mmol/l in women), a low serum iron (<7.1 µg/l), a low serum ferritin (storage form of iron) (<30 ng/l), a low transferrin saturation (<15%), and a high total iron-binding capacity (>13.1 µmol/l) (Kariyeva et al. 2003; Bermejo and Garcia-Lopez 2009; Clark 2009). The most crucial functions include its role in oxygen transport through its presence in hemoglobin and oxidative phosphorylation via electron transfer in cytochromes. In human body, iron is found in hemoglobin, myoglobin (within muscle fibers) and other tissues, and is stored within liver, bone marrow and macrophages (Conway and Henderson 2019). Iron deficiency can be broadly defined as a condition in which body lacks enough iron to cater its need or is not able to utilize available iron. Low iron supply in the body leads to the production of weakened red blood cells (RBCs) causing the IDA. It is a serious global public health problem that particularly affects young children and pregnant women, mostly in developing countries (Short and Domagalski 2013). World Health Organization (WHO) defines anemia as a condition in which the number of RBCs or the hemoglobin concentration within RBC is lower than normal. WHO has estimated that 42% of children less than 5 years of age and 40% of pregnant women worldwide are anemic (Department of Nutrition and Health Development, World Health Organization 2011). Among adolescents the worldwide prevalence of anemia is 15%, where as 27% in developing countries and 6% in developed countries (Balci et al. 2012).

The conceptual framework of the United Nations Children's Emergency Fund (UNICEF) on malnutrition indicates the causes of anemia are at three different levels—basic, intermediate and immediate. The basic causes are socio-economic, the intermediate cause is the lack of access to public health resources and immediate cause is inadequate dietary intake. Hence a policy level intervention is required to tackle anemia from the grass-root level (UNICEF 2015; *Call for action to scaling up nutrition*).

Body's iron requirements and its availability

Significance of iron in the body

Iron is an essential element for most living organisms as it participates in a wide variety of metabolic processes, particularly in delivering oxygen throughout the body by hemoglobin an essential protein component of RBCs. The majority of human iron stores are found in hemoglobin. Apart from oxygen transportation, iron is eminently involved in energy production, cellular respiration, DNA synthesis and the production of dopamine and serotonin, which are essential to

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Table 1. Heme containing proteins found in plant source.

S. No.	Plant globin	Plant origin	Distinctive characteristics
1	Non-symbiotic hemoglobin	Algae, Bryophytes, gymnosperms	Heme-Fe either penta- or hexa-coordinate. The penta or hexa-coordinate depends on number and interaction of heme with histidine Moderate to high affinity for O_2 Localized in any plant organ
2	Class/type 1 non-symbiotic hemoglobin	Angiosperms	Heme-Fe predominantly hexa-coordinated by a distal amino acid Extremely high affinity for O_2 mostly due to a very low O_2-dissociation rate constant Localized in any plant organ
3	Class/type 2 non-symbiotic hemoglobin	Angiosperms	Heme-Fe predominantly penta-coordinated Moderate to high affinity for O_2 Localized in any plant organ
4	Symbiotic hemoglobin	Non-legume, N2-fixing plants	Heme-Fe predominantly penta-coordinated Moderate to high affinity for O_2 Specifically localized in N_2-fixing nodules of actinorhizal plants or any other non-legume land plant
5	Leghaemoglobin Lb	N2-fixing legumes	Heme-Fe predominantly penta-coordinate Moderate to high affinity for O_2 Specifically localized in legume N_2-fixing nodules
6	Class/type 3 non-symbiotic hemoglobin/truncated hemoglobin	Algae and land plants	Globin-domain amino acid sequence and structure (i.e., folding into the 2/2-fold) similar to those of bacterial truncated haemoglobins Heme-Fe either penta- or hexa-coordinate Moderate to high affinity for O_2 Localized in any plant organ

neurotransmission (Muñoz et al, 2017; Miller 2013). The storage and transportation of iron are highly dependent on the morphology of RBCs and the presence of sufficient amounts of hemoglobin. Two third of total body iron is found in circulating erythrocytes in the form of hemoglobin, remaining iron is found in myoglobin of muscle tissue and several enzymes involved in cell functions mainly oxidative metabolism (Abbaspour et al, 2014).

Forms of iron in human diet

Dietary iron is present in two forms, heme iron and non-heme iron, with heme iron being absorbed from the gut with greater efficiency (Ramsay and Charles 2015). The greater efficiency of absorption is due to specific heme transporters which enable the heme iron to pass directly across cell membranes and into the bloodstream, whereas non-heme iron is unable to utilize these transporters, requiring reduction of ferric iron to ferrous iron prior to absorption (Young et al. 2018; Scientific Advisory Committee on Nutrition, 2010).

Heme iron

Heme iron comes from hemoglobin and myoglobin of animal meat (DeMaeyer et al. 1989). Heme iron is estimated to contribute 10%–15% of total iron intake in meat-eating populations, but, because of its higher and more uniform absorption (estimated at 15%–35%), it could contribute 40% of total absorbed iron. Major heme containing protein in animal sources are beef and chicken liver, lamb, oysters, clams, mollusks, mussels, beef, sardines, turkey, chicken, fish (halibut, haddock, salmon, tuna, etc.), ham and veal (Short et al. 2013; WHO 2001).

Other hemoglobin like proteins were discovered in plants and were defined as Phytoglobins but their concentration levels are significantly lower than heme iron found in meat. A classification system has been established (Hill, Hargrove, and Arredondo-Peter 2016; Kakar et al. 2010) (Table 1).

Non-heme iron

Non-heme iron, which is present in both plant foods and animal tissues, is usually less absorbed than heme iron. The absorption of non-heme iron in people is approximately 5%–12% of the iron listed on the nutritional label. Balance between absorption inhibitors and enhancers as well as iron status of individual plays important role in absorption of non-heme iron (Cook 2005; WHO 2001). Several food sources of iron rich plants and their iron content are listed in Table 2.

Factors influencing iron absorption

There are several food items and even drugs which directly or indirectly competes with absorption of iron in human body. Table 3 is compilation of most understood factors influencing iron absorption by our body. Insights of iron absorption and bioavailability of various iron sources help us understand and tackle iron deficiency problem. Efforts by various organizations at global level have been deployed to address this issue (Hurrell and Egli 2010; Blanco-Rojo and Vaquero 2019; WHO 2001; Geissler and Singh 2011; Abbaspour, Hurrell, and Kelishadi 2014; Kumar et al. 2020; SCAN 2010). Section 5 gives a broad view of these efforts.

Iron metabolism

Mechanism of iron absorption

Mechanism of absorption of these irons in the intestinal mucosal cells involves various transport processes and regulatory proteins. Several iron binding proteins such as transferrin, lactoferrin, hemoglobin, bacterioferritin, along with various other functional agents present at several key sites control the iron digestion in stomach. Duodenum is the principle site for iron absorption greatly influenced by the physical state of iron. The passage of iron from the intestinal lumen to the circulation through the enterocytes is defined as absorption. Iron absorption occurs by divalent metal transporter 1 (DMT-1), a member of the solute carrier group of membrane transport proteins. The uptake of elemental iron requires acidic conditions to aid the solubility of ferrous iron and to provide protons for co-transport via the DMT-1 (West and Oates 2008).

The exact mechanism of the utilization of absorbed iron in body is still not completely clear. It has been hypothesized that once the ferrous iron gets absorbed into the enterocyte cytoplasm, it can be utilized in one of following three ways: (1) It can get transferred to local mitochondria to produce heme molecules, (2) It can get transferred across the duodenal mucosa into the blood, where it is transported by transferrin to the cells or the bone marrow for erythropoiesis into ferritin and then stored within the enterocyte. Free iron binds to apotransferrin, a glycoprotein, forming the molecule transferrin, responsible for transporting and circulating iron in the plasma (Geisser and Burckhardt 2011). It binds iron that is released to the systemic circulation from duodenal enterocytes and macrophages. Transferrin supplies the erythroblasts in the bone marrow with circulating iron for erythropoiesis, to the tissues that require iron for growth and reparative processes. Transferrin also supplies the iron that binds to the storage molecules ferritin and haemosiderin, (3) It can get transported from the host cell to distant body sites. Ferric iron (Fe^{3+}) reduced to ferrous iron (Fe^{2+}) and then transported through the apical membrane of enterocytes. Iron transporter Ireg1 (SLC11A3, also known as ferroportin or Mtp1) facilitate the export of ferrous iron through the basolateral membrane of intestinal enterocytes (Petrak and Vyoral 2005). The release of ferrous iron from enterocytes by ferroportin is assisted by the copper-containing ferroxidase enzyme caeruloplasmin and in the intestine iron transport is facilitated by its membrane-bound counterpart hephaestin. These enzymes oxidize Fe^{2+} to Fe^{3+} before the iron binds to the iron-transport protein transferrin (Wallace 2016).

Table 2. Iron rich plant foods used in diet.

Food group	Food	Iron, mg/100 g contained in raw edible portion
Cereals and millets	Bajra (Indian millet, *Pennisetum typhoideum*)	6.42
	Panicum miliare	1.26
	Amaranth seed	9.3
Pulses and legumes	Soybean	8.29
	Chickpea, roasted	6.0
	Cowpea	5.9
	Lentil	7.6
	Peas, dry	5.09
	Horse-gram (Dolichos biflorus), whole	8.76
Green leafy vegetables	Amaranth, beet, gogu, fenugreek	7–10
Other vegetables	Lotus stem, dry	60.6
	Karonda, dry	39.1
	Sundakai, dry	22.2
	Onion stalks	7.4
	Plaintain greens	6.3
Nuts and oil-seed	Garden cress seeds	17.2
	Niger seeds	18.19
	Gingelly seeds	13.9
	Mustard seeds	13.49
Dry fruits	Pistachio nuts	4.5
	Dates	4.79
Condiments and spices	Turmeric	46.08
	Mango powder	45.2
	Black pepper, cloves, cumin	10-11

Heme iron transport mechanism

Heme iron is hypothesized to be taken up by receptor mediated endocytosis. Internalized heme is degraded by heme oxygenase (HO-1/2) inside the vesicles, releasing non-heme iron and generating biliverdin. The non-heme iron is then transported to the cytoplasm by DMT-1. Heme iron may also be taken up by PCFT/HCP1 directly into the cytoplasm. Intact heme may be transported across the basolateral membrane by heme transporter (FLVCR) where it binds circulating hemopexin. Alternatively, heme may be catabolized to non-heme iron and biliverdin by HO-1 located on the endoplasmic reticulum. Any iron released from heme inside the enterocyte, regardless of the mode of uptake, ultimately joins the labile iron pool and is transferred to the bloodstream by FPN1 in the same fashion as non-heme iron. Thus, food sources very high in hemoglobin are considered as an excellent nutrient source of iron as directly internalized Fe^{2+} is

Table 3. Factors influencing iron absorption.

		Major source and mode of action
Iron absorption inhibitor	Polyphenols	Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages: these form insoluble iron complexes in the gut
	Phytic acid	whole grain cereals, nuts: form insoluble phytate iron complexes in the gut
	Dietary supplements	Calcium, Zinc and other divalent metal: Disrupt the enterocyte transport mechanism to blood. Absorption of heme and non-heme iron is reduced
	Proteins	Whole casein, alpha 5 casein phosphopeptides: strongly bind iron and prevent its absorption
	Metabolic inhibitors, antibiotics	Antacids, H2 blockers and proton pump inhibitors. Quinolones and tetracycline antibiotics
Iron absorption enhancers	Ascorbic acid	Citric fruits, vegetables, juices: Forms soluble iron-ascorbate complexes which remain soluble in the intestine and facilitates reduction of Fe^{3+} to Fe^{2+}, favoring iron absorption
	Meat, fish and poultry	Iron binds to digestible factors (proteins) present in muscle tissue like peptides rich in cysteine residues and carbohydrate fractions formed during digestion of proteins have effect like ascorbic acid and glycosaminoglycans of the extracellular matrix of muscle tissues

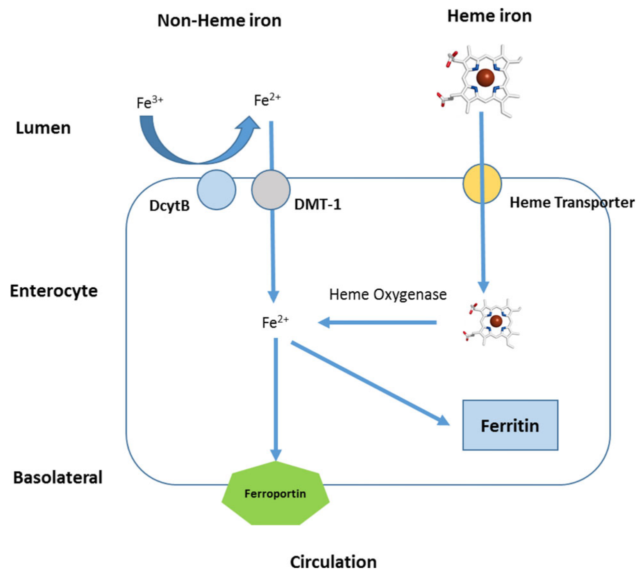

Figure 1. Iron absorption from heme and non-heme iron sources.

processed by the enterocytes and eventually exported across the basolateral membrane into the bloodstream via Fe^{2+} transporter ferroportin (Conway and Henderson 2019; Short and Domagalski 2013).

Non-heme iron transport mechanism

As non-hemic iron forms are insoluble, it cannot get absorbed and get excreted with the feces. In-order to get absorbed it must be converted to soluble form. Pepsin and hydrochloric acid action release the non-hemic iron, present in food component in the gastrointestinal tract during digestion. Non-heme iron exists in two forms: reduced ferrous (Fe^{2+}) and oxidized ferric (Fe^{3+}) forms. Ferrous forms can only be absorbed by duodenal enterocytes. Ferric form of iron needs to first be reduced to its ferrous form, this is taken care by cytochrome b reductase (duodenal cytochrome b) (Johnson-Wimbley and Graham 2011) or other reducing agents present in the apical membrane of duodenal enterocytes. Ferrous iron (Fe^{2+}) is rapidly oxidized to the insoluble ferric (Fe^{3+}) form at physiological pH. Fe^{3+} in the intestinal lumen reduced by ferric reductase due to lower pH of gastric acid thus allows the subsequent transport of Fe^{2+} across the apical membrane of enterocytes. This enhances the solubility and uptake of ferric iron. When gastric acid production is compromised, iron absorption is reduced substantially (Marx 1997). The ferric forms of iron rapidly precipitate in the intestine's alkaline medium thus ferrous forms of iron are much more soluble. The iron released by the gastric and pancreatic proteases action, binds to intraluminal ligands which stabilize the ferrous form, keeps the iron soluble and subsequently biologically available to be captured and transferred to the interior of the enterocyte (Short and Domagalski 2013; Aldallal 2016).

Thus, heme iron is much easily absorbed compared to the non-heme iron which requires various factors to get absorbed and utilized. Figure 1 illustrates both heme and non-heme iron absorption in enterocytes. Comprehending on both forms of iron absorption explains easier heme absorption compared to the non-heme iron which requires various factors to get absorbed and utilized.

Iron bioavailability

Bioavailability was initially correlated to absorption and was determined by *in vitro* solubility. Earlier, iron availability is calculated based on solubility of iron compound. Through various studies and understandings concept of iron bioavailability has now evolved and is currently defined as the amount of iron ingested that is absorbed by the intestine and used through normal metabolic pathways or stored and is expressed as a percentage of intake (Geissler and Singh 2011; Conway and Henderson 2019). Iron bioavailability is influenced by various factors like diet, environment and host. Iron bioavailability includes the following steps: (1) release from its matrix; (2) absorption into the systemic circulation; (3) distribution to tissues; d) metabolic utilization or storage in the body. Heme iron is unaffected by interaction with other food components hence contribute less toward the issue of iron bioavailability, however the heme form only constitutes 10%–15% of the dietary iron. All non-heme food iron that enters the common iron pool in the digestive tract is absorbed depending on the balance between the absorption inhibitors or enhancers and the iron status of the individual (Kumar et al. 2020).

Both forms of iron ferrous and ferric can be efficiently absorbed if these reach the mucosa in soluble form (Geissler and Singh 2011). Solubility plays a key role here, as ferric salts tend to precipitate when pH rises from the stomach to the duodenal area. This precipitation can be prevented by forming iron complexes with compounds that form absorbable chelates which are soluble at high pH. Dietary compounds that reduce iron from ferric to ferrous also generally increase bioavailability (WHO 2001; Cook 2005).

IDA prevalence

Global scenario

According to WHO, anemia affects 1.62 billion people globally, which corresponds to (24.8%) of the population. The highest occurrence is in preschool-age children (47.4%), and the lowest is in men (12.7%). However, most affected population group is non-pregnant women (468.4 million) (Department of Nutrition and Health Development, World Health Organization 2011). The WHO also classifies anemia as a major public health problem if the prevalence is more than 50% of any subset of the population (Department of Nutrition and Health Development, World Health Organization 2011). The latest available global data of anemia prevalence for the most affected population groups, i.e., pregnant women, non-pregnant women and children under 5 years by WHO, as represented in Figure 2, supports the above world population analysis.

Demand for iron is higher among pregnant women, and women with anemia in combination with early onset of child bearing, a high number of births, short intervals

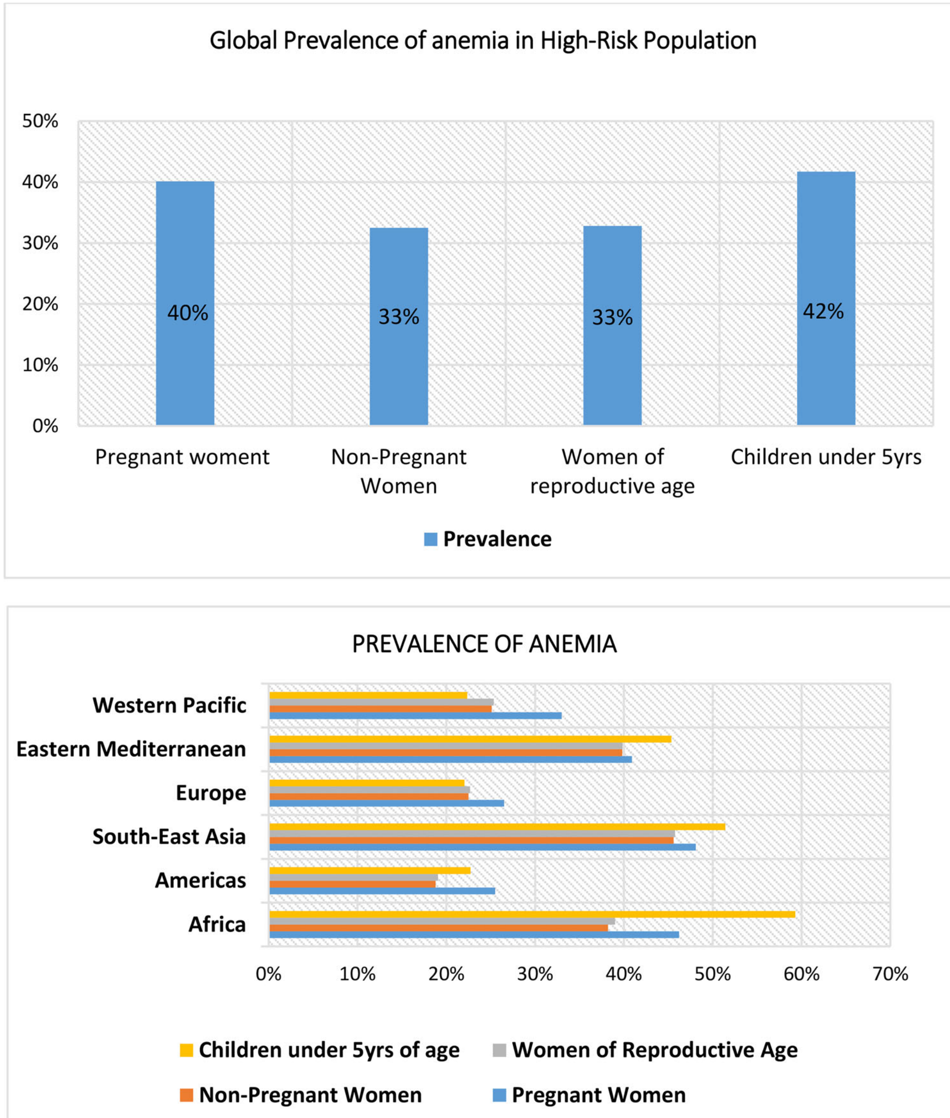

Figure 2. (a) Global Prevalence of Anemia in High-Risk Population. (b) Regional Prevalence of Anemia for subgroups. Data Source: WHO's GHO (Global Health Observatory: Indicator—Anemia; World Health Organization).

between births and poor access to antenatal care. According to WHO's Global Health Observatory (GHO) data, prevalence of anemia does not have a significant correction over decades (Global Health Observatory: Indicator—Anemia; World Health Organization). Figure 3 indicates global prevalence of anemia among women and young children. It is observed that there is no improvement in the nutritional status.

Anemia makes important contributions to the disease burden in most low- and middle-income countries. From 1990 to 2010 there was significant decrease in IDA prevalence, still anemia was responsible for 68.3 million years lived with disability (YLD) in 2010 which accounts 8.8% of the global data and more than depression, chronic respiratory disease and totality of injuries. It was observed that between 1990 and 2010 total anemia YLD increased in all ages. Increased prevalence and growth in population was responsible for causing YLD in young age groups whereas population aging is possibly responsible for increased YLD in older age groups, because anemia prevalence in these age groups decreased (Kassebaum et al. 2014).

Further scrutinizing the global scenario data from the above section, African, South-East Asian and East Mediterranean regions (WHO regions) have dominance of highly affected population. Excessive prevalence of anemia, from further analysis turns out to be amongst children below 5 years with African country Mali and Yemen in east Mediterranean region with 84% prevalence. Even though individual countries in east Mediterranean region like Yemen have higher prevalence of anemia between 60%–70% in all sub-group of women, average data of all countries indicates south-east Asia to be mostly affected. Women subgroups in India and Myanmar from south-east Asian regions are the largely affected population.

Global data indicates predominance of IDA in developing countries. Contemplating data from global heath repository, top most countries suffering from anemia for respective population groups have been summarized in Figure 4.

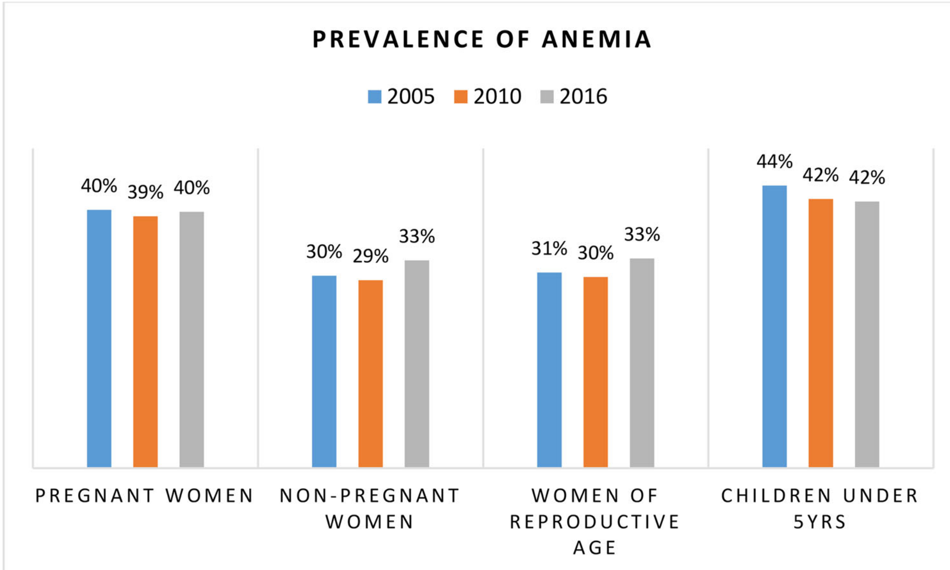

Figure 3. Global Health Observatory (GHO) data on prevalence of anemia in women and young children. Data Source: Global Health Observatory: Indicator—Anemia; World Health Organization.

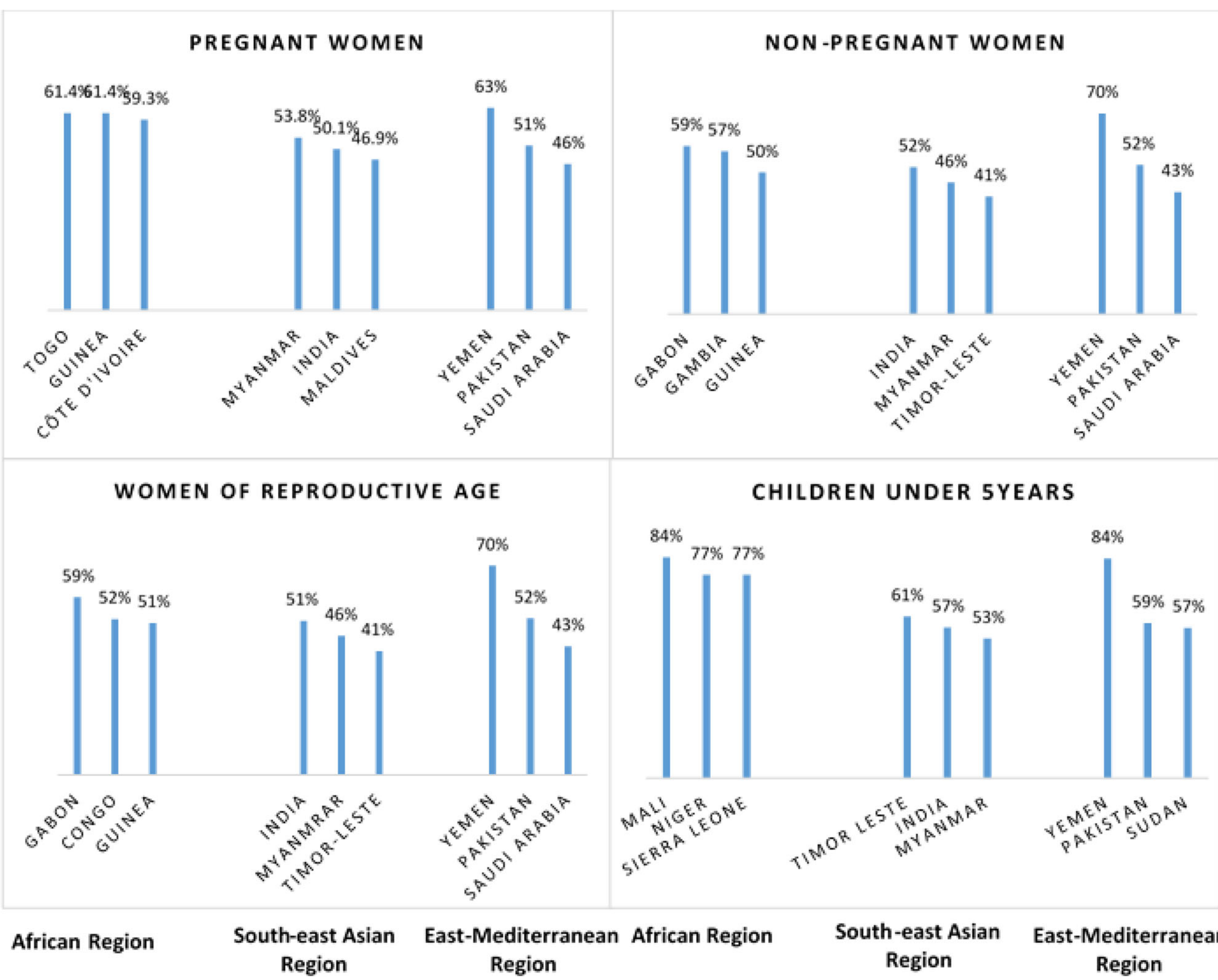

Figure 4. Prevalence of anemia in Countries from highly affected regions. Data Source: Global Health Observatory: Indicator—Anemia; World Health Organization.

Above data clearly specifies higher predominance of IDA in south-east Asian countries for women subgroup. India, Myanmar, Maldives, Timor-Leste and Bangladesh are the countries with topmost predominance of anemic condition in women population, with Indian women suffering the most.

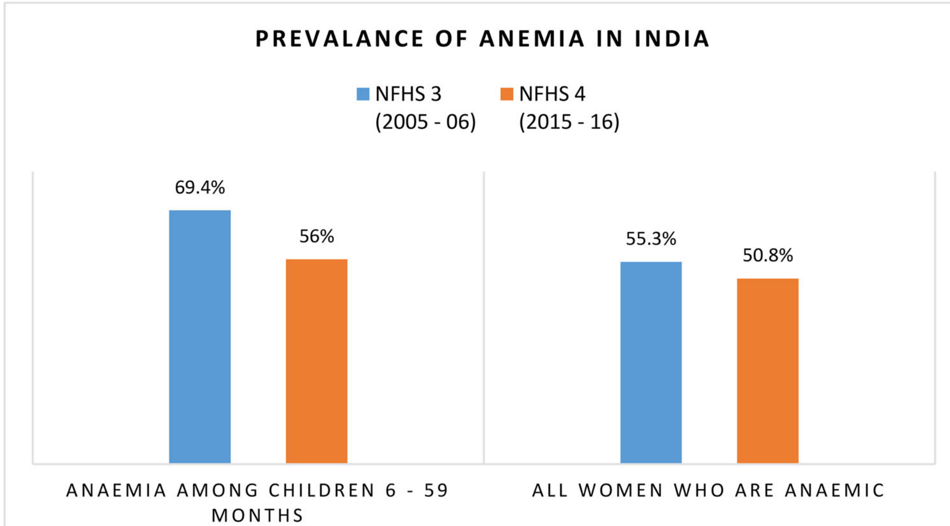

Figure 5. Prevalence of Anemia in India. Data Source: National Health and Family Survey (NFHS) IV, Ministry of Health and Family Welfare, 2015–16; National Health Policy, 2017.

Indian scenario

In India, 53% of all women have anemia (2015–16 National Family Health Survey). The persistent high level of prevalence of the disorder among women in India is a matter of great concern. The Ministry of Health and Family Welfare, Government of India, also acknowledges this as a major burden. According to the National Family Health Survey (NFHS), Figure 5 indicates the status of anemia (in percentages) over two decades (NFHS IV, Ministry of Health and Family Welfare, 2015–16; National Health Policy, 2017).

In 2018, the Comprehensive National Nutrition Survey (CNNS) conducted on girls aged between 10 and 19 years are anemic. This survey indicated 39.6% girls were anemic and out of those anemic girls, as high as 31.3% were having IDA (CNNS; Ministry of Health and Family Welfare, Govt. of India, 2019).

It is, therefore, evident that the Indian scenario also shows a similar trend as compared to the global statistics, over the last two decades and that there is no significant improvement in the status of IDA.

The Ministry of Health and Family Welfare and the Ministry of Women and Child Development have acknowledged the public health concerns on anemia. Despite decades long several global administrative measures phytic acid—discussed in following sections, the blood iron levels have failed to increase. This also indicates possibility of the presence of a physiological barrier, which needs to be identified yet (Timmers et al. 2020). The global and Indian data on the prevalence of IDA emphasize the need for understanding the underlying cause of anemia and developing strategies based on respective regions.

Consequences of iron deficiency

There are some medical consequences of Iron deficiency which may include disturbances in growth and development, infants with depressed immune function; reduced capacity for doing physical work and reduction in the cognitive performance at all phases of life. School going adolescents with IDA have found to be low in verbal learning, mental balance and low IQ as compared to those not having IDA (More et al. 2013, Kassebaum et al. 2014). Iron deficiency increases the perinatal risk for mother and infants mortality (Thompson 2007). As estimated 10%–20% of preschool children in developed countries, and 30%–80% in developing countries, are anemic at age of 1 year and will have delayed psychomotor development and impaired language and motor skills (WHO 2001). Iron deficiency also affects immune system, capacity of lymphocytes to attack infesting organism gets reduced which results in the lower concentration of cells causing cell mediated immunity in iron-deficient populations and ultimately increases the rate of infectious diseases (WHO 2001). Due to iron deficiency absorption capacity of other divalent heavy metals and toxic metals increases which leads to risk of heavy metal poisoning in children (Kassebaum et al. 2014). Therefore, it is very important to work on prevention and control of IDA.

Strategies for prevention of iron deficiency

Food habits in developing countries as well as in specific population subgroups in developed countries with a history of high occurrence of malnutrition do not satisfy adequate micronutrient share of the body. This occurs due to economic, cultural or physiological reasons, making the addition of micronutrients an appropriate intervention. Several approaches can be used for this purpose either alone or in combination.

Dietary diversification

Diversification-based iron supplementation of food rich in iron/fortification of food can help to restore iron deficiency in the body. Dietary modifications proposed are (1) increasing intake of iron rich foods, especially meat-based products supplemented by increasing consumption of fruits and

Table 4. Compilation of significant pilot programs in Indian states to counter IDA.

Agency	Region	Vehicle	Outcome
United Nations World Food Programme, 2017	Odisha	Iron fortified rice (12 mg of Ferric pyrophosphate) delivered to school going children through Mid-Day Meals	6% reduction in anemia was directly correlated to the fortification intervention
National Institute of Nutrition, 2009	West Bengal	3.3 mg Ferrous Fumarate per kg of iodized salt distributed to 212 women working in tea plantations	Significant improvements in hemoglobin and serum ferritin
Government of West Bengal along with Nutrition International, 2000	West Bengal	Iron, folic acid and vitamin A fortified wheat flour was distributed through the Targeted Public Distribution System (TPDS) as a pilot in one district	Significant reduction in anemia among the beneficiaries, over a period of 24 months.
St. John's Institute	Karnataka	Multiple micronutrient fortified rice: 12.5 mg iron, thiamin, niacin and folate delivered to school children over a 6 month period	Increase in hemoglobin concentration

vegetables rich in ascorbic acid to enhance non-heme iron absorption, and (2) reduced intake of inhibitors of non-heme iron absorption. Negative impact of Phytate, polyphenols, divalent metal ions like calcium and zinc in iron absorption has been observed. Due to the phosphate groups of phytate, iron forms iron phytate complexes and release of iron from these complexes is difficult. Major food polyphenols have inhibitory effect on iron absorption by iron chelation, calcium also interferes in non-heme as well as heme iron absorption at its initial uptake into the enterocytes. Proteins like casein, whey, etc. have also been shown to inhibit iron absorption. Various measures to modify diet as well as improve diet ingredients to enhance absorption and decrease the inhibitory impact of such compounds have been established (Hurrell and Egli 2010; Blanco-Rojo and Vaquero 2019). In order to reduce level of phytic acid, techniques such as germination and fermentation enhance iron bioavailability, as this promotes enzymatic hydrolysis of phytic acid in whole grain cereals and legumes by enhancing the activity of endogenous or exogenous phytase enzymes. Non-enzymatic methods are also followed, such as thermal processing, soaking, and milling, for reducing phytic acid content in plant-based staples and has been successful in improving the bioavailability of iron (Prentice et al. 2017, WHO 2001). Considering positive effect of these inhibitors on human biology, dietary modifications for enhancing iron absorption have been suggested which includes diet plans avoiding consumption of inhibitors along with or after iron rich food (Blanco-Rojo and Vaquero 2019).

Supplementation

Supplements have high concentrations of vitamins and minerals to provide large amounts of nutrients in single or multiple doses. Dietary supplements are tailored for the requirements of specific population groups and must be consumed in an informed manner. Supplement intake can be the best method of micronutrient consumption when the levels are dangerously low. Disadvantage of dietary supplements is low population coverage and acceptance. Therapeutic supplementation is the most common path adopted to correct established IDA. Iron preparations generally contain one of three iron salts: iron sulfate, iron gluconate, and iron fumarate; these are preferred because of the dual advantage of low cost and high bioavailability. However, significant gastro-intestinal side effects are observed in various population groups, despite high bioavailability. Elemental iron and folic acid (IFA) supplementation prophylaxes happen in regions where there is prevalence of severe anemia. IFA supplementation is given through the District Health Centers. The population includes school children, pregnant and lactating women with severe anemia. As per the NFHS IV, 77.7% of pregnant women were either given or purchased IFA supplementation during their pregnancy (NFHS IV, 2015–16).

The National Health Mission (NHM) under the Ministry of Health and Family Welfare (MoH&FW) has the weekly IFA supplementation (WIFS) program in place to reduce the prevalence and severity of anemia in adolescence. This program is implemented both in rural and urban areas. The beneficiaries are adolescent, school going children of 10–19 years, enrolled in government, government aided and municipal schools. Weekly Iron-folic Acid Supplements of 100 mg elemental iron and 500 μg of folic acid using a fixed day approach are administered. Further, the children are also screened for moderate to severe anemia and referred to appropriate health facilities. The WIFS program also includes bi-annual deworming and appropriate diet counseling to improve the dietary habits of the target population. This program currently covers 112 million beneficiaries (Operational Framework for weekly iron and folic acid supplementation, Ministry of Health and Family Welfare, Govt of India. 2012).

Food fortification

Fortification of foods with iron has been a commonly used strategy to combat iron deficiency throughout the world. In October 2016, a national level government consultation was held in India on food fortification. The success of various fortification pilots in the country was discussed.

Efficacy of fortification in India

Food fortification pilots have been successful in many instances in combating malnutrition. The pilot studies conducted by various national and international agencies have provided the government with solid evidence and expedited a policy level progress on fortification. Some of the significant food fortification pilots, which specifically targeted IDA

Table 5. Level of Iron fortification in flours in various African countries.

Country	Commodity	Iron compound and fortification levels
Ghana	Wheat flour	Ferrous fumarate, 58 ppm
Mali	Wheat flour	Ferrous fumarate, ferrous sulfate or electrolytic iron: 60 ppm
Nigeria	Wheat flour	40 ppm of NaFeEDTA
	Maize flour	40 ppm of NaFeEDTA
Kenya	Wheat flour	50 ppm of NaFeEDTA
	Maize flour	10 ppm of NaFeEDTA
South Africa	Wheat flour and maize flour	35 ppm of electrolytic iron

are summarized in Table 4 (Large Scale Fortification in India. Journey so far and road ahead. Food Safety and Standards Authority of India, 2018). Similar studies have also been conducted in various parts of the country. In most pilots, owing to consumption patterns and availability, the staple foods were the vehicles for fortification.

Global scenario: government policies and regulations

Various countries have mainstreamed food fortification into their legislations to combat malnutrition. Since fortification policies target mass consumption, currently the global food fortification targets staple commodities. The vehicles for fortification include milled cereal grains, oil, milk and salt. Milled cereals such as maize and wheat flour, and salt are ideal iron fortification vehicles (Bhagwat et al. 2014).

Citing the Food Safety and Standards Authority of India's advocacy document on fortification, globally 66 countries have mandated wheat flour fortification, 14 countries have mandated the fortification of maize flour and wheat flour (Large Scale Fortification in India. Journey so far and road ahead. Food Safety and Standards Authority of India, 2018).

USA

The United States published its fortification policy in 2015 (United States Food and Drug Administration. 21 CFR Part 104, Subpart B—Fortification Policy https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=104.20). The policy was framed in order to increase the nutritional quality of food supply in the US. The policy is designed taking cognizance of the daily recommended intake for various nutrients. The policy currently states that foods can be fortified with 2% of the daily requirement of the nutrient. The daily requirement of Iron for the US population is 18 mg, based on a 2000 Kcal diet. Hence the levels of fortification in a food must not be beyond 0.9 mg/100 Kcal.

The European Union

The legislation EC 1925/2006 governs the addition of nutrients to food. The legislation states that nutrients can be added to food considering the safe upper limits derived from scientific studies. The legislation also states that the member countries can mandate fortification of nutrients to food based on the nutritional requirements (European Parliament 2006).

Africa

Many African countries have a high burden of IDA. Multiple pilots have been done by various development partners in many African countries. Few examples of African countries who have mandated iron fortification in their mainstream food supply as listed in Table 5 (Food Fortification Initiative. Global Progress Monitor http://www.ffinetwork.org/global_progress/index.php).

India

The fortification regulations in India were framed with the backing of recommendations from Indian Council of Medical Research (ICMR). The formulations were set based on consumption levels, recommended dietary allowance (RDA) and permissible overages (The Food Safety and Standards Authority of India (FSSAI): Food Safety and Standards (Fortification of Foods) Regulations, 2018; Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India. Effective: August 15, 2016. https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/biologicals/CDSCO-DBT2016.pdf).

Standards have been published for five commodities—rice, wheat, double fortified salt, oil and milk. Rice, wheat and double fortified salt have recommended levels of iron to be added. On June 8, 2020 the standards of these fortified commodities have been marked as mainstream food standards (Table 6) (Food Safety Standards Authority of India (FSSAI). 2020. Government Advisories. https://fssai.gov.in/upload/advisories/2020/06/5edf277952c1bDirection_Fortified_Salt_Maida_09_06_2020.pdf).

Food fortification in India received a national momentum with Government of India's Eat Right Mission in 2016. In the same year, to commemorate the World Food Day on October 16, the Food Safety and Standards Authority of India published food fortification standards for five commodities.

India's social safety nets such as the Mid-Day Meal (MDM) scheme, Integrated Child Development Services (ICDS) and Targeted Public Distribution System (TPDS) have also adopted fortified commodities in their supply chain, in many states.

The FSSAI also constituted an independent Food Fortification Resource Center (FFRC) to support the state government and private sectors to promote fortified commodities into the supply chain. As a result, several retail outlets have a dedicated section for fortified staples. The consumption of fortified staples has also significantly increased. The FFRC's indicates the state-wise increase in availability and consumption of fortified commodities (Food Fortification Resource Center (FFRC). 2021. https://ffrc.fssai.gov.in/c-dashboard; https://ffrc.fssai.gov.in/state-performance).

As per the FFRC, 10 Indian states have mainstreamed iron fortification through their social safety nets through rice, wheat flour or double fortified salt. The targeted fortification interventions are based on the prevalence of anemia and evaluating the outcome on a continuous basis. While the current regulations include the fortification standards for commonly consumed staples, it is imperative that standards for packaged commodities and novel food is also accommodated in the regulatory framework.

Table 6. Iron fortification in table salt, wheat flour and rice.

Commodity	Fortificant	Remarks
Double Fortified Salt	Iron (As ferrous sulfate or ferrous fumarate) 850–1100 ppm	Iodine fortification is mandatory for salt, whereas iron fortification is optional
Wheat Flour (Whole and Refined)	Iron (As Ferrous citrate or Ferrous lactate or Ferrous sulfate or Ferric pyrophosphate or electrolytic iron or Ferrous fumarate or Ferrous BisGlycinate): 28–42.5 mg/kg Sodium Iron (III) Ethylene diamine tetra Acetate Trihydrate (Sodium feredetate-Na Fe EDTA): 14–21.25 mg/kg	World Health Organization recommends Sodium Iron EDTA as the synthetic iron with highest bioavailability.
Rice	Sodium Iron (III) Ethylene diamine tetra Acetate Trihydrate (Sodium feredetate-Na Fe EDTA): 14–21.25 mg/kg (or) Iron (ferric pyrophosphate): 28–42.5 mg/kg	In rice, EDTA is not compatible from a sensory perspective. Hence ferric pyrophosphate is the most common iron fortificant for rice.

Table 7. Characteristics of the Iron compounds used for food fortification.

Characteristics	Water-soluble	Soluble in dilute acids	Poorly Soluble in dilute acid	Chelate compounds	Encapsulated compounds
Examples of iron compounds	Ferrous sulfate	Ferrous fumarate	Elemental iron (reduced, electrolytic and carbonyl iron)	NaFe-EDTA, Ferrous bisglycinate	Encapsulated ferrous sulfate, Encapsulated ferrous fumarate
Reactivity with the food matrix	High	Intermediate	Very low	Low to intermediate	Low
Bioavailability relative to ferrous sulfate	Equivalent 100%	Equivalent 100%	Low 20%–50%	Equivalent to higher 100%–300%	Equivalent 100%
Cost based on iron content	Intermediate	Intermediate	Low	High to very high	Intermediate to high
Cost based on iron content and bioavailability	Low	Low	Intermediate	High	Intermediate

There is a huge potential for processed food and novel foods to address the micronutrient gap. This could be achieved through stakeholder consultations which involves in-depth analysis of the available evidence. Novel foods which are a source of essential micronutrients can also be accommodated in FSSAI's current novel food safety assessment framework (The Food Safety and Standards Authority of India (FSSAI): Food Safety and Standards (Non-Specified Food and Food Ingredients) Regulations, 2017). Generating evidence for efficacy of the fortified food could be one of the possible assessment points of such novel food. Eventually, food fortification from non-conventional food sources would be mainstreamed.

Foods that have nutrients added to them which are naturally not present in it, can be defined as fortified foods. The WHO Guidelines for food fortification distinguishes three approaches to food fortification: mass, targeted, and market-driven. In mass fortification, micronutrients can be added to the regularly consumed edible product. However, in targeted fortification, the food is designed for specific population subgroups, such as complementary weaning foods for infants, foods for institutional programs aimed at school children or preschoolers, and foods used under emergency situations (De Benoist et al. 2008). The scenario for market-driven fortification entails manufacturing food by adding one or two micronutrients to processed food primarily to increase sale. In addition to the mandatory nutrients mentioned in Table 7 which provides the level of iron fortification for various commodities, these can also be fortified with optional nutrients.

Science of food fortification

Fortification of foods with iron is more difficult than fortification with nutrients, as the most bioavailable iron compounds that are soluble in water or diluted acid often react with other food components to cause off-flavors, color changes or fat oxidation. Thus, less soluble forms of iron, although less well absorbed, are often not chosen for fortification to avoid unwanted sensory changes. Ferric pyrophosphate and ferrous fumarate addition in rice and wheat have showed significant ability to cure anemia. Iron supplemented with folic acid is also increasingly getting practiced (Table 4). Bioavailability of iron is a major research area being studied to make iron absorption more effective. Importance of bio-available iron is detailed in section 5.6 separately.

Stages in developing iron-fortified foods

Owing to the mass consumption and access, various government interventions to combat malnutrition would choose fortification of staple food commodities to deliver the nutrients. The market products also focus on fortified staples. However, more recently, processed food such as complementary food for infants are also entering the supply chain. There are three stages in food fortification with iron:

I. **Selection of the iron compound:** Iron compounds with greatest potential absorption and compatibility to the target food are selected, which after adding at the appropriate level, causes no undesirable sensory changes in either the fortified food or the final cooked product. The selection of iron compound must also take account of the existing regulatory limits.

II. **Optimization of iron absorption:** In order to meet nutritional needs absorption enhancers are added and wherever possible inhibitors are eliminated or reduced.Further, food processing conditions have to be optimized with adequate overages to ensure that the iron content remains constant throughout the shelf life of the food.

III. **Targeted:** There are two categories of iron compounds used for food fortification: inorganic iron compounds and protected iron compounds. The inorganic iron compounds that are mostly used in food fortification are classified as: (a) water-soluble, (b) poorly water-soluble/soluble in dilute acid, and (c) water- insoluble/ poorly soluble in dilute acid. Whereas protected iron compounds are classified as Chelate compounds and encapsulated compounds. Iron compounds used in fortification are listed in Table 4 with their characteristics.

Bio-fortification

Bio-fortification is the process of increasing the content and bioavailability of essential vitamins and minerals in staple crops, through plant breeding or agronomic practices, to improve nutritional status (Bouis et al. 2011). The aim of bio-fortification is to ensure that staple food crops have abundant micronutrients. Presence of polyphenols and phytic acid in plant derived foods impede the bioavailability of mineral nutrients significantly compared to foods from animal sources (Hurrell and Egli 2010). Bio-fortification combines traditional breeding with modern techniques. A sustainable and long-term approach for amelioration of nutrient deficiencies is possible by bio-fortification. Worldwide, the focus of bio-fortification programs is on iron, zinc, selenium and vitamin A. The aim of these programs is to either complementing as well as in some instances replacing chemical fortification or contributing to food supplementation. In grain seeds, iron is primarily located in the aleurone layer and embryos. Postharvest processes (such as polishing and milling) remove these tissues that contain iron. Various strategies can be applied to bio-fortify iron to various staple crops such as cereals like wheat, rice, and millets as well as to protein rich legumes (Prasad, Shivay, and Kumar 2014; Vasconcelos, Gruissem, and Bhullar 2017).

Commonly Used Strategies in Bio-fortification:

- Conventional Breeding

Traditional breeding relies on inheritance of a phenotype that expresses high iron, together with a very specific genetic marker (Rommens 2007). Modern cultivars of most crops have very less genetic diversity when compared with older landraces and wild ancestors (Esquinas-Alcázar 2005). To cite an example from the case of cultivated wheat, currently grown cultivars have relatively low iron levels (Fan et al. 2008). The downward trend in the concentration of iron continues as we see an increase in yield. Chromosomal regions from wild ancestors such as *Aegilops* have been introgressed into cultivated wheat resulting in the increase of grain iron over two-fold (Tiwari et al. 2010; Neelam et al. 2011).

Estimated Average Requirement or EAR is referred to as the median daily intake value calculated to meet the requirement of half the healthy individuals in different age as well as gender groups. Bio-fortified crops developed by conventional breeding have the potential to provide an extra amount in the range of 20 to ≥100% of EAR for specific nutrients The average addition to the EAR is ∼25% for zinc crops, 35% for iron crops, and >85% for provitamin A crops; Bouis and Saltzman 2017; Anderson et al. 1996; FAO HarvestPlus 2019).

As part of the HarvestPlus program (https://www.harvestplus.org/; FAO HarvestPlus 2019. Biofortification: a food-systems solution to help end hidden hunger. http://www.fao.org/publications/card/en/c/CA8711EN/), the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) jointly with the Mahatma Phule Krishi Vidyapeeth, an agricultural university in the state of Maharashtra, India, developed a high-iron variety of pearl millet, called *Dhanashakti*. This variety was released in 2012 in Maharashtra and subsequently, in 2013 across India. Thus, it was the first mineral bio-fortified product of any crop cultivar released in India. *Dhanashakti* has 71 mg/kg iron and 40 mg/kg zinc. Another high-iron pearl millet hybrid (ICMH 1201) was developed by ICRISAT. This is marketed as *Shakti 1201*. This hybrid has 75 mg/kg iron and 40 mg/kg zinc (similar to *Dhanashakti*), but it has more than 30% higher grain yield than *Dhanashakti* with much higher iron content than the best bio-fortified rice varieties (less than 5 mg/kg). Also, many, but not all, have much higher iron content than the best bio-fortified wheat varieties (less than 40 mg/kg) (Govindaraj et al. 2019).

- Recombinant DNA technology

Very little genetic variation in iron concentration in the endosperm of staple cereal grains has been observed. Consequently, transgenic approaches may be one of the options of obtaining varieties with increased iron (Connorton and Balk 2019). Genes involved in different steps of iron homeostasis such as uptake, transport, storage and regulation have been studied extensively both individually as well as in a combination. Leads for adopting the most effective promoter-gene combination are available. These leads can assist in planning a feasible and appropriately effective program for achieving bio-fortification using genetic modification (Connorton and Balk 2019).

Transgenic rice with enriched Fe and Zn has been possible with the identification of key genes involved in the uptake, translocation, and storage of these two minerals (Wirth et al. 2009; Bashir, Ishimaru, and Nishizawa 2010; Ishimaru, Bashir, and Nishizawa 2011) In a single event, up to 15 ppm increase in Fe and up to 45 ppm increase in Zn were observed in polished grain of an elite variety. What was significant is the absence of uptake on unwanted heavy metals (cadmium, arsenic, and lead) (Trijatmiko et al. 2016; Wu, Gruissem, and Bhullar 2019). The level of Zn in this genetically modified rice was considerably higher than in the Zn enhanced varieties that were developed by conventional breeding (Van Der Straeten et al. 2020).

Indian regulations on rDNA based bio fortification

All forms of GM foods (ingredients, additives, processing aids) are regulated by the Department of Biotechnology ('Rules for the

Table 8. Recombinant DNA technology approaches for improving heme.

Approach	Strategy and genes involved	Host organism	Aim and reference
Effect of metabolic engineering of the heme biosynthetic pathway	Over expression of HEM2, HEM3 and HEM12, along with over expression of globin gene HBA (coding α), HBB (coding β) and HBAA (coding di-α) were synthesized and codon optimized	*S. cerevisiae*	Improved hemoglobin production in yeast; Liu et al. (2014)
	Co-expression of BP450, a Cys-ligated heme protein and HBPAS: a His-ligated heme protein with Ferrochelatase (FC) (from *E. coli*)	*E. coli*	Enhances heme content; Sudhamsu et al. (2010)
	Co-expression of Ferochelatase FC and gsNOS (*Geobacillus stearothermophilus* nitric oxide synthase)	*E. coli*	Enhances heme content; Sudhamsu et al. (2010)
	Co—expression of Hug A/B/C/D, TonB, and Exb B/D (*Plesiomonas shigelloides*)	*E. coli*	Henderson et al. (2001)
	hemA (*Salmonella typhimurium* LT2) & hemL(*E. coli* BL21) in recombinant DyP (from *B. subtilis*)	*E. coli*	Improved catalytic activities of a dye-decolorizing peroxidase (DyP); Ramzi et al. (2015)
	Iba ORF from *G. max* (soyabean)	*C. reinhardtii*	Improved bio-hydrogen production. Wu et al. (2011)
	Codon-optimized hemH (*Bradyrhizobium japonicum*) and Iba gene (*Glycine max*)	*C. reinhardtii*	Improved bio-hydrogen production; Wu et al. (2010)
Co-expression with globin genes	Co-expressed α and β globin genes	*E. coli*	Hoffman et al. (1990)
	Co-expression of alpha and beta-globin genes(human) and the methionine aminopeptidase (Met-AP) gene from *E. coli*	*E. coli*	High yield of hemoglobin;Shen et al. (1993)
Expression of globin genes	glbN gene (*Synechocystis sp.* PCC 6803)	*E. coli*	Scott and Lecomte (2000)
	Lb1 gene (*Lupinus luteus* sp.)	*E. coli*	Sikorski et al. (1995)

Manufacture, Use, Import, Export and Storage of Hazardous micro-organisms/Genetically engineered organisms or cells, Department of Biotechnology, 1989) though a move to partly permit this is now in abeyance since 2011 (S.O.2478[E] dt.4/10/2010 that keeps S.O.1519 dt.23/08/2007 in abeyance 'till further notification). The FSSAI has also restricted the use of heme iron from animal sources for food fortification (Direction under Sec.16(5) F.No.VIP Ref/Fortification/FSSAI dt.31/05/2018 ; https://fssai.gov.in/upload/advisories/2018/03/5a9796d988f70209.pdf). However, DBT, GEAC and CDSCO have approved the production and sale of rDNA drugs (https://geacindia.gov.in/approved-products.aspx) mainly erythropoietin and its variants for treatment of anemia related to renal failure (https://geacindia.gov.in/approved-products.aspx; Drugs imported and marketed in India (https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTUzNQ==).

Erythropoietin is a protein hormone essential to production of RBCs (erythrocytes), which themselves deliver oxygen to all tissues in the body. This hormone is synthesized in the kidney and its secretion is regulated by the amount of oxygen delivered to that organ (Kelkmann 2013; Kurtz 2017). Erythropoietin was one of the first drugs produced through recombinant DNA technology and is widely used in conditions where RBC production is deficient In India, production of erythropoietin as a biosimilar is regulated under regulations that are generally similar to the guidance of the European Medicines Agency (EMA) which has the longest track record for assessment of biosimilars, dating back to the 2003 EMA regulatory framework, and the initial EMA approvals of these products in 2006 (Bennett et al. 2014).

Alternate approach

Alternate approach from above strategies is use of cell factories for enhancing and producing heme and hemo-proteins having iron in a form that can be easily absorbed. Myriad of studies on expressing heme in different organisms ranging from bacteria, fungus and microalgae have been done. The typical example of bio-fortification is genetic manipulation of rice. Several varieties of rice developed which are rich in Vitamin A, beta-carotene, zinc, iron and folate (Singh, Gruissem, and Bhullar 2017; www.goldenrice.org). These cell factories have fast reproduction rate, ease of accessibility to their genetic material and possibility of correlating the expression of a gene in the intact cell with its expression in a system composed of highly purified components, and hence provide a suitable platform for heme synthesis. Few of the approaches and examples have been collated in the Table 8.

Dark side of iron

Iron is an essential mineral. Our body has tightly controlled mechanism of iron absorption in digestive track. This regulation also keeps check on over-absorption of iron.

Free heme offers toxic effects to tissues and organs through oxidative stress by generating ROS and redox-active iron of heme plays the central role for heme toxicity. Iron loading results in the generation of toxic hydroxyl radicals causing damage by lipid peroxidation, oxidation of amino acid side chains (especially cysteine), formation of protein–-protein crosslinks and oxidation of polypeptide backbones, leading to protein fragmentation, DNA damage, and DNA strand breaks (Abbaspour, Hurrell, and Kelishadi 2014; Yuen and Becker 2020).

Though supplements are the best way to rapidly increase iron levels, acute intake of more than 20 mg/kg iron from supplements or medicines can lead to gastritis, constipation, nausea, abdominal pain, vomiting, and faintness, especially if food is not taken at the same time. Taking supplements containing iron above certain level can also reduce zinc absorption and plasma zinc concentrations. Iron deficiency can be prevented by iron supplementation, but, when taken with zinc, there is a significant reduction in zinc absorption

(Harvey et al. 2007). Supplemental iron taken during lactation may impair zinc absorption. Decrease in zinc absorption in pregnant women prescribed with higher dose of iron supplements throughout pregnancy (120 mg/d) and lactation (76 mg/d) was observed (Chung et al. 2002). Several studies showed that iron supplementation resulted in lower plasma zinc concentrations. When high iron containing trace minerals given in solution can negatively affect zinc absorption in adults (Whittaker 1998). In severe cases overdoses of iron can lead to multisystem organ failure, coma, convulsions, and even death. Iron toxicity can be either sudden or gradual. Accidental overdoses, taking high-dose supplements for a long time may lead to many serious health problems. Transferrin protein limits presence of free iron in our blood by directly interacting with it. However, iron toxicity can significantly increase the levels of "free" iron in the body. Free iron is a pro-oxidant and may cause damage to cells. Too much iron can have the opposite effect and increase the risk of infections as elevated levels of free iron stimulate the growth of infecting bacteria and viruses (WHO 2008).

Iron toxicity can occur when people, usually children, had overdose of iron supplements, excessive absorption of iron from food or high levels of iron in food or drinks. When the body's regulatory system fails to keep iron levels within healthy limits it leads to gradual build-up of too much iron in the body referred as iron overload. For most people, iron overload is not a concern. Individuals with hereditary hemochromatosis absorb excessive iron from digestive tract. The higher absorption of iron leads to risks of arthritis, cancer, liver problems, diabetes and heart failure. Studies also suggest that heme-iron may raise the risk of colon cancer. There is no effective mechanism to reduce iron load from body. Regular blood donation and menstrual blood loss in women reduces iron over-load risk (Yuen and Becker 2020).

Conclusion

Iron deficiency and anemia are most prevalent in general population today. As various metabolic processes utilize iron, understanding about various iron sources, forms and metabolism will help in combating iron deficiency issues globally. Traditionally, especially in earlier times, food were cooked in iron vessels. The slow release of iron during cooking process seems to have fortification effect in food but determination of iron concentration and bioavailability is questionable. More often such practices are neither validated nor documented. A deeper study on cooking and slow release of metal irons in food can be an area of interesting study.

According to WHO, even after implementing various strategies, there is no significant improvement in body iron levels globally. Along with implementing strategies like food/diet-based effort and supplementation, a thorough follow-up and introducing new programs for regions with high prevalence is of utmost importance. Efforts in food fortification has enhanced worldwide but is less approachable in developing countries. Modern technology has opened avenues for bio-fortification and have been widely implemented for various crops. With advancement in biotechnology and use of transgenic approaches, delivering micronutrients to populations that may have limited access to diverse diets can now be made possible. Considering the bioavailability and absorption factors of non-heme iron sources and toxicity of high dosage of iron, efforts toward expressing heme source of iron in different hosts have been initiated. There are issues with this approach since it involves the use of genes from animal sources, making its consumption restrictive to the highly affected population groups. To overcome this, proteins from plants akin to hemoglobin and myoglobin and classified as Phytoglobins are now becoming most sought out approach. As concentration of these proteins naturally is scarce, attempts to express these proteins in various hosts like bacteria, yeast and algae have been made. Successful attempts for enhancing these protein expressions have been achieved in bacteria and yeast and advancement of expressing protein from algae or in algae have been made. These efforts have the promise of being highly sustainable strategies than just food-based, supplement-based or fortification-based approaches as absorption of these proteins will be much higher than any other strategies combined. Refining these approaches in accordance to regulatory policies can be one of the futuristic approaches to decrease iron deficiency globally.

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Conflicts of interest

The authors declare no conflict of interest.

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