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Understanding and Addressing the High Prevalence of Anemia in India: Nutritional, Interventional and Monitoring Challenges

Review Article

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Abstract

Anemia is a global health concern characterized by lower than normal levels of hemoglobin, which affects approximately 30% of the world population. India contributes towards a large proportion of the total globally affected. Low dietary intake of iron is a primary cause for anemia prevalence in India. Despite nationwide efforts such as oral supplementation programs and fortification of food, the prevalence of anemia continues to rise, according to India's 5th National Family Health Survey. This review focuses on highlighting the limitations of current intervention practices, while exploring alternative strategies that could be potentially adapted in conjunction with existing measures. It is crucial that drawbacks in existing monitoring and diagnostic practices towards examining population susceptibility and reporting accurate demographics of iron deficiency and anemia in India be assessed. Finally, this review also illustrates the efficacy of adaptable household measures in determining the nutritional status at both community and national levels.

Keywords: Iron Deficiency; Anemia; Iron Deficiency Anemia; IDA; India; Nutrition; Food Processing; Fortification; Intervention; Iron Status

Introduction

Anemia is a globally prevalent clinical condition, which is characterized by lower than normal levels of red blood cells (RBC) and hemoglobin (Hb) in the blood stream [1]. This condition limits the amount of oxygen reaching cells and tissues of the body. Typical symptoms of anemia include fatigue, dizziness, shortness of breath, headache, pale or yellow skin, and irregular heartbeat. Depending upon the causative factors that contribute to a depletion of RBCs, anemia has been classified into different categories, amongst which iron-deficiency anemia (IDA) is the most prevalent form of this condition that affects nearly 30% of the global population [2]. Currently, the segment of the global population that is most susceptible to anemia is constituted by children under five years of age, menstruating women belonging to adolescent and adult age groups, pregnant women, and postpartum women. Factors that subject women to a higher risk of developing IDA include blood-loss during menstruation and childbirth, as well as the growing demand of iron to nourish the fetus in pregnant women. Moreover, severe IDA during pregnancy carries a 'high' risk of premature delivery, often leading to underweight infants, or in worse cases infant and maternal death [3].

Developing nations such as India are subjected to a greater burden of anemia prevalence within the population, in comparison to their 'developed' counterparts. As per the National Family Health Survey 5 (NFHS-5) conducted in India between 2019 and 2021, anemia affects roughly 67.1% of children between 6-59 months of age, 59.1% of adolescent women between 15-19 years of age, and 52.2% of pregnant women between 15-49 years of age in India [4]. The numbers have only continued to rise among all segments of the population since the previous NFHS-4 conducted between 2015 and 2016 (Figure 1). It wasalso highlighted that India contributed towards approximately 80% of all maternal deaths due to anemia in South-Asia, while, 58% of all lactating Indian women were anemic [3]. A low dietary intake of iron has been regarded as the primary cause behind such a massive prevalence of anemia among Indians [5]. Iron deficiency among women and children in India is a major nutritional concern, which is often caused by insufficient dietary intake of iron to make up for the iron utilized towards physiological and metabolic needs.

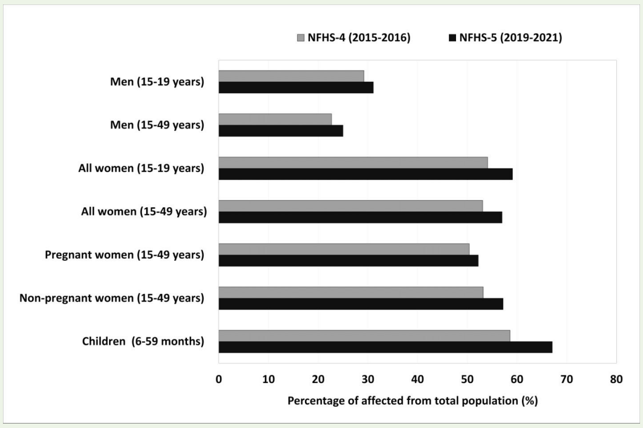

Figure 1: Percentage (%) of the total population affected by anemia in India as reported in NFHS-5 (2019-2021) and NFHS-4 (2015-2016). The data has been shown for seven different categories of the population [4,127].

Although, the alarming rise in anemia within the Indian population has acquired the interests of the government, non-governmental organizations and researchers alike, efforts towards promoting iron supplementation and routine diagnostic testing have not succeeded in effectively decreasing the percentage of the affected population. Concurrently, there is a lack of comprehensive research literature that accurately links the current demographics to its real drivers, which would otherwise enable appropriate responses to be formulated. Anemia may also result from underlying chronic inflammatory diseases, genetic mutations, vitamin B12 deficiency, infections, and autoimmune diseases [6, 7]. However, Indian efforts towards mitigating the burden of anemia has been largely restricted to the diagnosis and treatment of IDA, with disregard to the existence of other forms of anemia. It is worth noting that the Indian population is ethnically diverse with a rich genetic diversity and varying genetic predisposition to different clinical conditions. Moreover, different cultural groups engage in varying lifestyles that includes heterogeneity in sources of nutrition and cooking methods.

Current relevant questions include whether the number of reported cases of anemia are accurate, what percentage and distribution of total cases of anemia are in fact the result of iron deficiency, why is the occurrence of iron deficiency high despite oral iron supplementation programs, and what other forms of institutional and/or household interventions apart from oral supplementation could be adapted to address this nation-wide increase in anemia? So far, these questions have eluded sufficient attention from the scientific and policymaking communities. This review seeks to highlight the role of Indian dietary patterns on anemia prevalence and elucidate the shortcomings in existing interventional strategies, while exploring both conventional and novel solutions that could potentially mitigate the burden of anemia in India. Additionally, this literature also provides an overview of the drawbacks in current diagnostic practices to determine anemia and iron deficiency across the Indian population to promote the reporting of more accurate and representative demographic data. In total, 129 references were reviewed for the purpose of this study.

Pathogenesis of Ida

Iron (Fe) is an essential micronutrient, which forms a key component in the structure and activity of oxygen-transporting proteins, Hb and myoglobin (Mb) [8]. Iron is primarily stored in the form of ferritin, a protein that is synthesized by hepatocytes, macrophages and enterocytes [9]. The iron balance is determined by the amount of iron consumed through diet, the physiological requirements of the individual and the amount of iron stored as ferritin [10]. 'Iron deficiency' refers to a drop in the levels of total-body iron, which translates to a depletion of the iron reserves stored in macrophages and hepatocytes. This state of depleted iron stores often precedes the onset of 'anemia', which is marked by a decrease in Hb and RBC levels in blood. Anemia typically occurs due to loss of RBCs from the body, inefficient RBC production in bone marrow, and/or hemolysis of RBC [11].

The pathogenesis of IDA can be differentiated into three characteristic stages [11]. The first stage is characterized by depleting levels of body iron that may arise due to a multitude of reasons including inefficient absorption from meals or blood-loss during menstruation, which promotes the utilization of storage iron (ferritin) to meet the requirements of erythropoiesis. Following the exhaustion of storage iron, during the second stage, erythropoiesis occurs in a state of iron deficiency, wherein production of Hb and myoglobin becomes limited. This stage is often labelled as 'iron deficiency without anemia', since erythrocytes maintain morphological structure, and circulating hemoglobin levels remain unaffected. Moreover, an increase in transferrin/total iron binding capacity (TIBC) and a decrease in % saturation of transferrin is noted during the second stage [12]. Transferrin refers to the iron transporting molecule, the measurement of which represents the total iron binding capacity (TIBC) of blood, while TSAT refers to the percentage of TIBC that is bound by serum iron. Prolonged deficiency of iron in the body inevitably leads to IDA, which is marked by reduction in the levels of Hb below normal and marks the third stage. The inadequate levels of Hb leads to the development of hypochromia and microcytosis in erythrocytes. Therefore, it is crucial to diagnose early onsets of iron deficiency in segments of the population who are at a higher risk of developing IDA.

Clinical conditions such as polycystic ovarian disease (PCOD) and polycystic ovary syndrome (PCOS) subject women to a higher risk of developing iron deficiency and anemia. While both conditions are related, PCOS is generally considered a much broader and more severe, since it affects both endocrine and metabolic functions, where symptoms include hormonal imbalance, insulin resistance, infertility, menstrual irregularity, hirsutism, obesity, and cardiovascular diseases. Although not fully understood, anovulation is widely regarded as the starting point, which subsequently develops cysts and inflammation in the ovaries, before a spike in androgen secretion is observed [13]. PCOS has been shown to confer iron deficiency and anemia among women in two different ways. Firstly, irregular or excessive menstrual bleeding may lead to iron deficiency and subsequently anemia. Secondly, chronic inflammation and oxidative stress related to the

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symptom of obesity in PCOS patients upregulates the production of hepcidin, which in turn restricts the absorption of iron in the small intestine, inadvertently leading to iron deficiency [14].

Thyroid disorders such as hyperthyroidism (overactive thyroid) and hypothyroidism (underactive thyroid) also predominantly affect a large percentage of women. Hypothyroidismis often accompanied by anemia, which is caused by different biomolecular mechanisms. During hypothyroidism, low levels of thyroid hormones fail to promote erythropoiesis due to a decrease in erythropoietin gene expression, which decreases RBC levels [15]. Additionally, hypothyroidism also decelerates metabolism rateto inflict gastrointestinal changes, whereinfood passes at a slower pace within the digestive tract. A slow digestive process coupled with decreased gastric acid production inhibits the absorption of iron, folate, and vitamin B12 in the intestine, which may lead to iron deficiency and anemia. It has also been documented that hypothyroidism may result from pre-existing iron deficiency and its associated anemia. Thyroid peroxidase is an important enzyme in the synthesis of thyroid hormone, the activity of which is largely regulated by iron as a cofactor. During iron deficient conditions, the activity of thyroid peroxidase is down regulated, which suppresses thyroid hormone production [16].

Diagnostic Approaches

Numerous blood-based molecules and cells serve as biomarkers in the diagnosis of iron-deficiency and anemia [17]. Based upon biomarker concentrations in blood, respective stages of iron deficiency and anemia may be diagnosed. In clinical settings, a complete blood count (CBC) test is ideally the first test performed, which determines the count of RBCs, Hb, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), leukocytes, and platelets from blood samples. The red blood cell indices from CBC tests serve as a proxy indicator of iron status in individuals [18]. The periodical NFHS in India primarily measures the hemoglobin levels of a large number of sample populations to determine anemia prevalence. However, it was concluded that the sole focus on Hb levels obtained through CBC tests only managed to detect anemia, and failed to discriminate between subjects with normal iron status and those with iron deficiency "without" anemia [18]. Furthermore, low Hb concentrations may also result from other forms of anemia such as folate or vitamin B12 deficiency, and hence is not an IDA-specific biomarker [19]. Other parameters of CBC such as MCV, MCH, and RDW have practically shown inconsistent sensitivity and specificity in detecting early onsets of iron deficiency [18, 20].

A serum ferritin (SF) test is often recommended following a CBC analysis to determine the iron status of an individual with low Hb levels [21]. The physiological role of ferritin in iron storage makes it highly sensitive to changes in iron levels in serum. Therefore, its quantification enables detection of iron deficiency with greater sensitivity, as compared to CBC parameters, especially in the diagnosis of early onsets of iron deficiency, preceding anemia. The extracellular ferritin concentrations measured in serum is secreted by macrophages [22]. Although, the lower cutoff values of serum ferritin enable diagnosis of iron deficiency, underlying conditions of inflammation may result in elevated levels of this biomarker, which may misguide the interpretation of results in patients [23]. Hence, complementing serum ferritin tests with a measure of transferrin saturation (TSAT) is recommended to alleviate the possibility of iron status overestimation. The serum iron bound to transferrin is primarily utilized for the purpose of erythropoiesis, and hence provides a reliable measure of iron status in patients. However, the relatively higher cost and lower accessibility of SF tests in India have led to a wider application of CBC tests in clinical settings, which fails to account for existing iron deficiency within the population, the prolongation of which may lead to anemia.

Additionally, the point-of-care testing (POCT) device "HemocueHb 201", used during NFHS-4 and NFHS-5 to measure Hb levels from capillary samples, has been shown to generate data that are less accurate and precise, as compared to hematology analyzers [4, 24, 127]. Furthermore, a study highlighted that the WHO recommended Hb cutoff values for anemia led to an overestimation of the percentage of anemia-affected population during NFHS-5 [25]. This deviation was attributed to the fact that the WHO cutoff values, which were based on studies conducted on North American and European populations, predominantly of ethnic white backgrounds, to not have been representative of the Indian population. Therefore, a reevaluation of the Hb cutoff values to suit the age and gender variations specific to India was proposed, which accounts for ethnic variations in physiological demands, geographical differences, and the prevalence of other pathological conditions. Similarly, a reexamination of SF cutoff values to account for the widespread occurrence of infections and inflammatory conditions in India, along with considerations for geographical and ethnic differences would allow accurate measurement of iron status in India. In India, where CBC tests are more accessible and affordable than SF tests, a combination of multiple CBC parameter cutoffs is recommended to accurately discriminate between the diagnosis of iron deficiency and IDA.

Genetic Predisposition To Iron Deficiency Anemia

Some rare forms of anemia arise due to genetic mutations in particular genes or as genetically inherited disorders. Iron Refractory Iron Deficiency Anemia (IRIDA) is an inherited autosomal recessive disorder that inhibits the absorption of iron from diets [26]. Oral supplementation of iron during conditions of IRIDA shows marginal improvement in the iron status of an individual. It is typically caused by a mutation in the Transmembrane Serine Protease-6 (*TMPRSS6*) gene, which encodes for proteolytic enzyme "Matriptase-2" [27]. This enzyme plays a key role in the negative regulation of hepcidin, which in turn regulates the homeostasis of iron in the body [28]. The role of hepcidin in the iron metabolism has been described as the peptide responsible for the degradation of ferroportin during conditions of iron overload [29].The knockout of *TMPRSS6* gene (*TMPRSS6*$^{-/-}$) in mice elevated hepcidin production, resulting in inhibited absorption of iron into intestine and blood plasma, which resulted in a substantial reduction in the plasma iron levels and transferrin saturation [28]. Additionally, *TMPRSS6*$^{-/-}$ mice displayed hallmarks of anemia such as hypochromia, anisocytosis, and poikilocytosis, validated by a depletion of red blood cell indices.

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Genome-Wide Associations Studies (GWAS) have been extensively performed to identify single nucleotide polymorphisms (SNPs) of *TMPRSS6* in human populations. So far, approximately 50 SNPs have been identified, among which the occurrence of rs855791, rs4820268, and rs11704654 has been studied most widely and linked to poor iron status[30, 31]. A study on SNPs of *TMPRSS6* and respective Hb levels in European and Indian Asian ethnic populations revealed that the 'A' allele of rs855791 associated with low Hb levels, was more frequently observed within the Indian Asian population, as compared to Europeans [32]. Moreover, another study highlighted the occurrence of 'A' allele of rs855791 with an additional reduction of 0.07 g/dL and 2.24 μg/L in the Hb levels and ferritin concentrations, respectively, in Asian population, as compared to Caucasian population [33]. The high frequency of this allele increases the susceptibility of Asian ethnic populations to IDA. More recently, an evaluation of an iron-deficienct pediatric cohort in the Indian subcontinent reported that 38% (23 patients) of the total iron refractory patients (60 patients) showed IRIDA phenotypes, among which 12 out of 23 cases demonstrated intronic and exonic variations [34]. However, to elucidate the genetic predisposition of the Indian population to IRIDA, further GWAS must be conducted, which accounts for the variations in SNPs and their occurrence in different ethnic groups of the Indian subcontinent. So far, six frequently occurring SNPs have been identified in the Indian population (Table 1). However, risk alleles of identified SNPs among the Indian population have not been extensively studied yet.

Table 1: Single nucleotide polymorphisms (SNPs) of the *TMPRSS6* gene observed within Indian subjects [128]

SNP	Mutation Type	Major Allele	Minor Allele
rs9610643	Intronic	A	G
rs855791	Missense/Exonic	G	A
rs78174698	Exonic	G	A
rs2543519	Intronic	A	G
rs2072860	Intronic	A	G
rs5756516	Intronic	C	T

The data represented in (Table 1) has been adapted from the study conducted by MohdAtan et al. (2022), licensed under Creative Commons Attribution 4.0 International License, which allows unrestricted use, distribution, and reproduction of results. (License link: Reprints and Permissions; About the license: Attribution 4.0 International)

Existing therapeutic strategies for IRIDA have focused on countering the oral iron refractoriness through intravenous (IV) administration of iron into bloodstream [35]. While a progressive improvement in Hb count, which may or may not lead up to its normal levels is typically observed upon IV iron administration, itresults in only partial correction of IRIDA. This long-term therapy fails to address the effects ofmicrocytosis and the low levels of transferrin saturation that are characteristic to IRIDA. In order to develop a holistic approach towards the treatment of IRIDA, recent research efforts have been directed towards identifying biomolecular targets involved in the pathogenesis of this condition. A group explored the possible therapeutic implications of silencing hepcidin by employing antibodies, which target the inhibition of Hemojuvelin (HJV) protein co-receptor involved in the production of hepcidin [36]. This study observed a significant improvement in Hb levels of *TMPRSS6*$^{-/-}$ mice upon IV injection of anti-HJV antibody (h5F9-AM8), with a peak in Hb levels being attained at 2 weeks from administration, followed by a gradual decline through week 8. Moreover, no histopathological abnormalities were observed in the spleen and liver upon IV administration of antibodies. Although rare in occurrence, refractoriness to oral iron supplementation poses a major challenge in treating IRIDA. Therefore, further research towards elucidating novel biomolecular participants in the pathogenesis of this disorder is crucial.

Current Intervention Strategy

Primary interventional strategies against anemia in India have been limited to oral supplementation of iron among at-risk segments of the population [37]. Oral iron and folic acid (IFA) supplements in the form of tablets is an age old interventional strategy, which was first implemented in 1970 through the launch of 'National Nutritional Anemia Prophylaxis Program' (NNAPP) by the Government of India with the objective of combating anemia at a community level. In recent years, the NNAPP has integrated with newer programs such as 'Anemia Mukt Bharat' (AMB), 'National Iron Plus Initiative' (NIPI), and the National Health Mission's (NHM) 'Weekly Iron Folic Acid Supplementation' to improve overall community outreach and extend its network nationally. NIPI recommends dosage ranging between 20mg to 100mg of elemental iron in combination with folic acid. The efficacy of iron supplementation has been well established, where clinical trials reported increase in Hb levels of patients, who took iron supplements for a period of three months [38].

Yet, the occurrence of anemia has only increased within all segments of the population since NFHS-4, which was conducted between 2015 and 2016 (Figure 1). Lack of compliance within the population plays a hindering role towards the efficacy of oral supplementation programs. Some influencing factors for poor compliance include undesired side-effects, gastrointestinal discomfort, unclear dosage instruction, poor counselling from prescriber, pseudo-scientific beliefs, forgetfulness, and a lack of general awareness among consumers about the implications of anemia towards maternal and child health [3]. Furthermore, misguided public perception of oral supplements as a form of medicine discourages continuation of its consumption after clinical improvements are noted [39]. Therefore, there is a need to incorporate additional measures in conjunction with oral supplementation, which is suitable and acceptable to the large and diverse population of India.

Dietary Sources of Iron

Through diet, iron is primarily acquired in two different forms:heme iron and non-heme iron [40]. The biomolecular mechanism by which both these forms of iron are absorbed into the duodenal cells vary. 'Heme' is a prosthetic group, which provides functionality to Hb molecules. Consisting of a ferrous (Fe^{2+}) cation surrounded by a porphyrin ring, heme iron is ideally found in animal-based foods such as red meat, poultry meat, liver and fish. Heme iron is absorbed into the enterocytes by transporter protein "Heme Carrier Protein 1" (HCP1) in the duodenal region of the small intestine [41]. Inside the enterocytes, heme iron is oxidized by the heme oxygenase enzyme to release the Fe^{2+} cation from the heme molecule [41].

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On the other hand, in the intestinal lumen non-heme iron typically exists in the ferric form (Fe^{3+}), which is unable to cross the intestinal membrane due to its insolubility in the intestinal pH. Absorption of non-heme iron into enterocytes is preceded by the reduction of ferric cations (Fe^{3+}) into its ferrous form (Fe^{2+}) by ferrireductase enzyme 'duodenal cytochrome B' (DcytB) [42]. Subsequently, Fe^{2+} ions are transported into the enterocytes by the activity of the divalent metal transporter 1 (DMT1), a transporter protein that lines the brush-like border in the inner wall of the small intestine. Non-heme iron is abundant in plant sources of food such as pulses, nuts, legumes and dark green leafy vegetables. Unlike heme iron, which is readily absorbed into the intestinal membrane, non-heme iron is comparatively less bioavailable; a characteristic attributed to the precipitation of ferric (Fe^{3+}) iron from aqueous solutions in the alkaline conditions of the intestinal lumen [42]. Moreover, the additional step involving the reduction of Fe^{3+} to Fe^{2+} to allow transport across the intestinal membrane makes the absorption process slower.

The dietary trends of the Indian subcontinent is diverse owing to variations in cultural practices, social identity and religion [43]. This heterogeneity, which includes variety in the type and quantity of ingredients used, as well as different cooking methods across subsets of the Indian population poses a significant challenge in summarizing the Indian diet into an average form [44]. These characteristic differences in the mode of nutrition plays a significant role in defining the iron status in terms of bioavailability, within different subsets of the Indian population. However, if food sources are to be considered, the traditional Indian diets across most regions are primarily vegetarian, with the inclusion of vegetables, grains and fruits, while animal-based food products such as dairy, meat, fish and eggs are variably consumed in a limited manner [44]. Apart from social constructs, the unaffordability of meat due to its high cost and lower incomes among consumers also contributes significantly towards its marginal consumption [5,44]. In the Indian diet, non-heme iron constitutes approximately 95% of total iron consumed [44, 45]. This may be indicative towards the fact that even among meat consumers, a large proportion of the total iron is acquired through plant sources of non-heme iron, which contributes to lower rates of absorption.

Dietary Factors Affecting Iron Bioavailability

The rate of non-heme iron absorption is largely affected by the components of the food matrix. Such components may include macro and micro-nutrients, fiber, polyphenols, and antinutrient factors such as phytates. Depending upon whether iron absorption is up-regulated or down-regulated, these components may be classified as enhancers or inhibitors, respectively. Some examples of enhancers include ascorbic acid (vitamin C), citrates, alcohol, and organic acids, while phytates, fiber, polyphenols, and vegetable proteins may act as inhibitors of iron absorption. The total iron absorbed by an individual is greatly influenced by the final bioavailable content of iron, which is determined by the net effect of all enhancers and/or inhibitors on the total iron content in their diets.

The impact of alcohol consumption on iron absorption is multifaceted; it has been shown to both enhance and inhibit iron absorption under varying conditions. Alcohol consumption has been linked to diminished production of hepcidin in the liver, which ultimately elevates serum iron levels [46]. The inhibitory effect on hepcidin production has been attributed to alcohol-induced oxidative stress and the formation of reactive oxygen species (ROS), which subdues the transcription of hepcidin. However, excessive alcohol consumption has also been found to increase risks of iron deficiency and anemia. Prolonged alcohol consumption is the cause for internal bleedings within the gastrointestinal system, which causes loss of erythrocytes [47]. Additionally, alcohol negatively affects the process of hematopoiesis in bone marrow, thus inducing anemia.

Depending upon its source, protein affects the bioavailability of iron differently. Proteins derived from plant sources, dairy sources, and eggs play an inhibitory role towards iron absorption, while animal sources of protein enhance iron absorption. Phosvitin is a protein, primarily found in egg-yolks, which inhibits iron absorption [48]. It is a highly phosphorylated protein with high-affinity towards iron, which causes formation of insoluble complexes, thereby limiting iron bioavailability. Protein from cow's milk such as casein demonstrates an inhibitory role in the absorption of iron by virtue of phosphoserine groups present within its structure [49]. Casein forms strong bonds with iron, which prevents iron absorption in the duodenal region of the intestine. Additionally, calcium is abundantly present in milk, which competes with iron for transportation across the intestinal membrane via DMT1. On the other hand, animal proteins native to muscle tissues have been found to significantly enhance iron absorption [50]. Cysteine and histidine amino acid residues within the structural configuration of muscle proteins bind iron to form soluble complexes, which aids absorption.

Ascorbic acid in diets: Ascorbic Acid (Vitamin C) is a water-soluble antioxidant, which functions as an enhancer of iron absorption in the small intestine. As a reducing agent ascorbic acid facilitates the reduction of Fe3+ ions into Fe2+ form, which is readily absorbed into the intestinal cells [51]. Additionally, the chelating property of ascorbic acid promotes the formation of soluble complexes with iron, which subsequently improves the solubility and bioavailability of iron in the intestinal pH [52]. In a study investigating the influence of fruit juices on iron absorption from rice meals, it was observed that the ascorbic acid content of juices was positively associated with the extent of iron absorption [53].

In contrast to single-meal studies, a diminished effect of ascorbic acid on iron absorption was noted in complete diet studies, which was attributed to the broad biochemical composition that is representative of total diets [54]. A possible dampening effect of the residual gastric contents from previous meals in a total diet on the activity of ascorbic acid was proposed. Moreover, it was revealed that ascorbic acid only conferred a prominent increase in iron absorption when consumed with meals, which naturally contained high content of iron absorption inhibitors such as phytates and polyphenols [55-57]. Additionally, a study of serum ferritin levels indicated that optimal absorption only occurred when ascorbic acid was consumed during meals, while consumption away from meal time or in between meals did not improve iron status [58].

It is imperative that the efficacy of ascorbic acid towards improving the iron status of the Indian population be studied, while accounting for the population's diverse dietary trends and consumption patterns. Studies of complete diets translate more closely to real-life dietary

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habits, which until now have shown marginal improvement in iron status, when consumed in conjunction with ascorbic acid. Further examination of Indian whole diets and its effects on the efficacy of ascorbic acid towards enhancing iron absorption is called for. In a largely plant-based Indian diet, the consumption of vitamin C is encouraged, since it has been shown to mitigate the iron absorption inhibiting effects of phytates and polyphenols present in plants.

Tea consumption in India: Tea (*Camellia sinensis*) is a popular beverage consumed by cultures across the globe. Although, drinking of tea has been associated with numerous health benefits such as improvement of cardiovascular health, antioxidant activity, and anti-inflammatory properties, tea consumption has been shown to lower the bioavailability of iron in meals. Phenolic compounds such as tannins, which are present in substantial amounts in tea inhibit the absorption of iron in the intestinal lumen by chelating iron to form insoluble complexes [59]. Thus, in the presence of polyphenols from tea, the amount of free iron available for absorption in the intestinal lumen decreases significantly.

India is the largest consumer of tea and holds place as the second-largest producer of tea globally. Although, the per capita consumption of tea is lower in India when compared to the global standards, nearly 88% of Indian households spanning across all socio-economic classes consume this beverage. A survey conducted by the Tea Board of India, which aimed to assess the trends in domestic consumption of tea reported that roughly 80% of tea drinkers consume tea before or during their breakfast, which is often the first most nutritious meal of the day [60]. Although there is a lack of comprehensive literature which focuses on the correlation of tea drinking with iron deficiency, especially among Indian tea drinkers, the extent to which the absorption of non-heme iron could be reduced by the consumption of tea alongside iron-fortified meals has been demonstrated to be around 79-94% in a previous study on human subjects [61]. In a separate study, it was observed that iron absorption was lowered by approximately 75-80%, when tea was consumed within an hour from a meal [55].

The role of tea as a potential cause for widespread iron deficiency and IDA within the Indian population warrants further investigation and appropriate public health interventions. Currently, a literature search focusing on the impacts of tea consumption on the Indian iron status reveals little information. A 50-70% drop in iron absorption was observed in Indian women between 18-35 years of age, irrespective of their pre-existing IDA or iron replete (control) status [62]. However, this study merely attempted to highlight the implications of tea consumption on two groups: women with IDA and an iron replete control group. These groups were selected based on specific criteria and subjected to a number of restrictions, which included consumption of only test meals and cutting off of vitamin-mineral supplements, which may not be representative of real-life scenarios. Another cross-sectional study on schoolchildren from Kerala, India, reported anemia among approximately 34.2% of tea/coffee drinkers, and 26.9% of non-drinkers [63]. There was however no comparison of the difference in severity of anemia between the tea/coffee drinkers and the non-drinkers, as well as no information regarding the ratio of tea drinkers to coffee drinkers among the anemic cases. Additionally, an overview of other enhancers/inhibitors of iron absorption within the regular diets of the anemic tea/coffee drinkers was absent, which would have allowed to determine if anemia prevalence in schoolchildren was in fact related to tea consumption.

Hence, the results of such studies may not be wholly relevant in a wider population-based model such as India, especially in terms of the heterogeneity and complexity associated with age, gender, diet, genetics and iron status. To accurately conclude if tea consumption in India is indeed a major driver of iron deficiency and IDA, several long-term randomized control trials need to be conducted [64]. Although, physiological adaptation of the iron metabolism by up-regulating or down-regulating iron absorption in response to an individual's iron status has been well documented, it is still not entirely clear as to what extent the body's adaptive responses to normal or depleted iron stores affect intestinal iron absorption in the presence of tea polyphenols [65, 66].

Dietary Diversification

A household measure towards improving nutritional status encompasses active consumption of a wide variety of foods that are rich sources of various nutrients. This practice is referred to as dietary diversification, which ensures a balanced intake of all essential nutrients, and has been recognized as a diet of "good quality" [67]. Dietary diversification has been positively associated with improved micronutrient status in populations [68]. The extent to which the iron status of a population may be improved through dietary diversification is determined by the net iron available for absorption in diets. Hence, dietary diversification should take into account the sum of total iron content consumed from a variety of foods, the type of iron consumed based on its source, as well as the presence of enhancers and inhibitors of iron absorption in diets.

Numerous studies have defined dietary diversity as a proxy indicator of micronutrient status. One such study determined that Ethiopian children, who consumed lesser than four groups of food per day were more likely to develop anemia than children who consumed diets of greater variety [69]. Additionally, South Ethiopian pregnant women with low dietary diversity were found more likely to be anemic than those with highly diverse diets [70]. Hence, a diverse diet is recommended as a long-term approach to improve the iron status of populations. The added advantage of dietary modification to ensure diversity is that it achieves adequate intake of multiple micronutrients and thereby, eliminates multiple nutritional deficiencies in the process.

However, the predominantly plant-based diet of the Indian population lacks diversity, wherein households rely on a few sources of staple grains and vegetables with limited consumption of animal products [71]. Such "dietary monotony", especially reliance on mostly non-heme iron sources inadvertently leads a population to absorb insufficient iron, which may subsequently lead to iron deficiency and anemia. Dietary diversity in India is largely influenced by a plethora of socio-economic factors. A study focusing on both rural and urban households in the Indian state of Uttar Pradesh established a positive relationship between household income levels and dietary diversity [72]. This observed relationship was consistent with results from a similar study on pregnant women from Kenya [73]. The correlation was explained by increased accessibility and affordability to a wider range of food sources with improving financial conditions. Moreover,

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a direct positive association was noted between the amount and size of land owned by rural Indian households, and dietary diversity, since land in a rural setting constitutes a financial asset from which, revenue may be generated [72].

Another socio-economic determinant of nutritional adequacy and dietary diversity within households is level of education, wherein maternal education level plays a key role towards the extent of nourishment in children under five years of age. A higher level of education typically correlates with a greater dietary diversity, and vice versa. Education typically determines the level of dietary diversity in two different ways: through its direct influence on employability and income levels of an individual or a household, and/or through health literacy [74]. The prevalence of iron deficiency and its related anemia in a large segment of India's rural population can be attributed to an absence of diverse diets, which in turn stem from issues relating to levels of income, education, and accessibility to iron-rich food groups. Therefore, the need for interventions to improve India's iron status goes beyond simple dietary diversification.

Impacts of Food Processing on Iron

Most diets across the globe involve pre-processing and processing/cooking of food before consumption in order to extend shelf-life, enhance digestibility, eradicate pathogenic microorganisms and toxic chemicals for food safety, increase bioavailability of nutrients, and improve 'palatability'. Based on the nature of transformation of food, processing techniques may be categorized as physical (grinding, peeling, emulsification, spray drying, etc.), chemical (refining, gelation, stabilization, etc.), and biochemical (fermentation, sterilization, pasteurization, etc.). These physical, chemical and biochemical changes subsequently alters the structural and functional characteristics of food, which affects the bioaccessibility and bioavailability of its components. Likewise, the amount of bioaccessible and bioavailable iron present in food may increase or decrease based upon the cooking or processing technique employed.

The diverse set of traditional cooking methodologies characteristic to the Indian household, coupled with novel processing/cooking techniques such as microwave and air-frying, ultimately determines the percentage of iron content in raw food that remains available for absorption in the small intestine. Conventional cooking methods in India entail frying, boiling, roasting, pressure cooking, and steaming [75]. Some pre-processing and processing techniques include soaking, sprouting, fermentation, dehulling, milling, and blanching. Each method affects the concentration and bioavailability of iron differently (Figure 2).

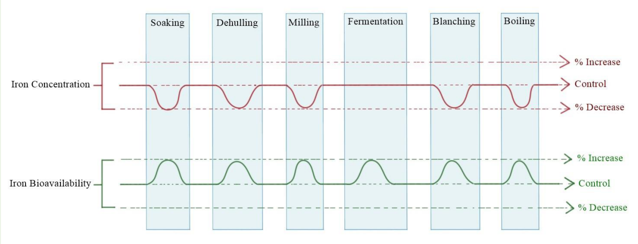

Figure 2: Percentage (%) increase and decrease observed in total iron concentration and iron bioavailability of food upon subjecting to six different food pre-processing and processing techniques

Soaking& Germination: Soaking is the practice of immersing foods such as legumes, nuts, and grains in water with the aim of softening, cleaning and improving its palatability. Sprouting is a similar process in which the legumes or grains are soaked, drained, and rested until the seeds germinate. Soaking and sprouting have been shown to improve the bioaccessibility of iron in legumes and grains [76]. Dephytinization is a process in which the phytate content of plant-based foods are lowered or removed to improve bioaccessibility and bioavailability of minerals. The presence of water activates an endogenous phosphatase enzyme in plants known as phytase, which in turn hydrolyzes phytate by the removal of phosphate molecules [77]. Thus, soaking and sprouting brings about a reduction in the level of phytates present in plant cells, thereby improving the bioaccessibility and bioavailability of iron in plant-based diets.

A study noted a 28.2% and 39.8% decrease in iron content upon soaking of green and white faba beans, respectively [76]. However, the phenomenon was attributed to the leaching out of iron into the soaking medium, which could be retained for further use to minimize iron loss. Additionally, the same study reported an increase in bioavailability of iron of both types of faba beans upon soaking and sprouting. Moreover, a reduction in the phytate content of both green and white faba beans was noted. The mechanism behind such reduction of phytate content in this study has been explained by a combination of the activity of endogenous phytase enzyme, as well as water solubilization of phytic acid salts [76].

Dehulling: Dehulling refers to the process of removing the "hull", the outermost covering of seeds, legumes and grains in order to improve texture and digestibility of food. The removal of hull around the kernel may be achieved by methods of grinding, rolling and pounding. The hull houses a variety of antinutrient factors such as polyphenols, phytates, and fibers, which limits the bioavailability of iron. Moreover, the hard outer covering of hull inhibits the bioaccessibility of iron stored within the kernel. Therefore, dehulling confers a significant improvement in the bioaccessibility and bioavailability of iron in plant-based foods. A previous study focusing on dehulling of four different types of legumes, namely cowpea, green gram, lentil, and chickpea demonstrated a substantial decrease in phytic acid and tannin content by 47-52 % and 43-52 %, respectively [78]. These results implied that a considerable amount of anti nutrients were present in the outer covering. Although the iron content of legumes decreased upon dehulling, which was attributed to a large proportion of the mineral being stored in the hull, dehulling improved the bioavailability of remaining iron.

Milling: Milling refers to the process of grinding, crushing, or pulverizing grains, seeds, and nuts to convert into powdered forms such as flour and ground spices. This technique also serves to separate components of seed and grains for the purpose of refining. This process is often carried out following dehulling, in order to further refine the dehulled products. In refined grains, the milling process removes the bran and the germ from the seed to leave behind the endosperm, whereas, whole grains consist of all three components intact. While whole grains are a great source of fiber, proteins, vitamins, and even minerals, which exist in high concentrations within the bran, these grains also house substantial amounts of polyphenols and phytates within the bran, the presence of which effects the bioavailability of iron.

Several studies have reported statistically significant reduction in the phytic acid content of cereal grains upon the removal of their bran through the process of milling [79]. However, milling also contributed to the loss of essential micronutrients such as iron which may be present in high concentrations within the bran. Milling of rice resulted in a reduced content of iron, as compared to brown rice with their brans intact [80]. Furthermore, the iron content of rice cultivars were negatively associated with respect to milling durations. The net change in total iron absorbed from milled food products, when compared with unmilled wholegrain food products, is determined by the total decrease in iron content and total increase in iron bioavailability following milling. Therefore, as a measure to ensure a net positive change in total iron absorbed, food products often undergo post-milling iron fortification.

Fermentation: For thousands of years, fermentation has been utilized and developed as a popular processing technique to produce a wide variety of food and beverages. Some popular applications of fermentation include bread making, cheese making, wine production, beer brewing, and yoghurt fermentation. By definition, fermentation refers to the metabolic pathway of anaerobic respiration in microorganisms, by which carbohydrate (substrate) is converted into organic acids, alcohol and carbon dioxide. Depending upon the type of substrate and microorganism utilized, the products vary significantly. Fermentation has been shown to improve the bioaccessibility of iron in cereals and legumes in multiple ways. Microbial phytase, as well as endogenous phytase in plants have been shown to hydrolyze phytates during fermentation [81]. Secondly, the action of phytase and α-amylase enzymes disrupts the complex phytate and starch matrix, inside which iron remains embedded [82]. In addition, organic acids synthesized as a by-product during fermentation lowers the pH to an optimal level for iron to solubilize. The low pH also provides favorable conditions for enzymatic degradation of phytate [81, 82].

Extensive studies have demonstrated the negative correlation between fermentation and phytate content in a number of cereals and legumes. One of the studies reported a 60% reduction in the phytic acid content of four different Sudanese sorghum cultivars upon fermentation for 12 hours [83]. The effects of fermentation on the bioaccessibility of iron was assessed in three popular Indian breakfast foods, Idli (rice : black-gram = 2 : 1), Dosa (rice : black-gram = 3 : 1), and Dhokhla (chickpea : green-gram : black-gram : rice = 2 : 2 : 1 : 1) [84]. The fermented batters consisting of rice and black bean combinations in idli and dosa oversaw an increase in iron bioaccessibility by 276% and 127%, respectively, while no improvement was observed in dhokhla batter. Additionally, tannin content of all three types of fermented batter was completely removed, while phytate content was reduced differentially. However, dhokhla batter recorded the lowest reduction in its phytate content among all batters, where a considerable amount of phytate remained after fermentation. This observation was attributed to the addition of chickpea and green gram to the rice and black gram combination, which added to the phytic acid content of the batter.

Blanching: Blanching is a pre-processing technique, wherein food is rapidly heated to a preset temperature, usually through brief immersion in boiling water or steam, before subsequently cooling it down rapidly to halt the cooking process. This technique is primarily employed towards preserving food through enzyme inactivation at high temperatures, retention of organoleptic properties, improvement of food texture, and prevention of microbial contamination. Types of food that are commonly blanched include vegetables, legumes, nuts, fruits, seafood, meat, and poultry. The physical and metabolic modifications in food cells due to blanching makes the membranes more permeable, which inevitably causes loss of water-soluble vitamins and minerals through leaching [85]. The extent to which micronutrients may be lost is largely determined by the set temperature and time in blanching, the maturity and variety of food, the blanching medium, cooling medium, and surface area to volume ratio of cut pieces of food.

Blanching of 12 species of Nigerian vegetables for 5 minutes in boiling water resulted in a 14.1% to 45.4% reduction in iron concentration [86]. However, blanching is also responsible for a reduction in the levels of antinutrient factors such as tannins and phytate, which significantly improves the bioavailability of iron [87]. A study demonstrated 53.7% to 73.8% and 46.23% to 88.47% reduction of phytic acid and tannic acid concentrations, respectively, in the leaves of cabbage, collard, turnip, sweet potato, and peanut, upon blanching for 10 minutes at 98±1°C [88]. In order to retain much of the iron content of raw food, blanching for a short duration is recommended. Blanching time has been negatively correlated with the mineral content of food [89]. Novel blanching techniques such as 'dry blanching', which eliminates the use of liquid blanching mediums have gained popularity in the food industry due to prevention of iron leaching. Other novel blanching methods include microwave blanching, infrared blanching, and high pressure blanching. The use of microwave blanching was shown to retain a greater percentage of phytochemicals in potatoes, as compared to conventional blanching with water [90].

Boiling: Boiling is a common method of cooking across the world, where food items such as vegetables, grains, legumes, and meat are submerged in a boiling solvent (primarily water) until it reaches a desired level of consistency (texture, thickness, hardness, etc.). Much like blanching, boiling is responsible for the loss of a significant amount of micronutrients, including iron [91]. In fact, boiling contributed to a greater loss in micronutrient content as compared to blanching, since boiling is performed for a greater duration of time to allow complete and thorough cooking of food. The same group compared the effects of three cooking methods, namely microwaving, blanching, and boiling on the iron content of spinach, brussel sprouts, and broccoli [91]. Boiling resulted in the highest percentage of iron losses among all three cooking methods at 52, 28, and 60 percent for spinach, brussel sprouts, and broccoli, respectively. However, since iron loss occurs primarily through leaching into the boiling medium, the retention of the boiling medium (stock) for further cooking or serving allows the lost iron to be retained [92].

Cooking with Iron Utensils: The use of iron utensils in various cooking practices have shown increased iron content in food, and led to improved Hb levels [93]. Iron from utensils leach out into the

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cooking medium to increase its total iron content. Therefore, it has been recognized as a cost-effective method, suitable for tackling iron deficiency and IDA in low-to-middle income countries. The extent to which iron content of food may increase is determined by the pH of food, the moisture/water content of food, as well as the cooking duration [94, 95]. The use of lemon in distilled water, which produced an acidic pH (pH = 3.2) demonstrated the highest leaching of iron when cooked in iron utensils, as compared to meals prepared in higher pH [94].

Additionally, the rate of leaching of iron into food is also dependent upon the age of the iron cooking ware [96]. The efficiency of iron utensils in enriching food with iron tends to decrease with usage, and frequent use accelerates the ageing process. Although, iron utensils have been a popular choice of cooking utensil in Indian households, adaptable strategies to optimize the extraction of iron from these utensils are still not widely known. Awareness about the benefits of utilizing iron utensils, along with methods of cooking to maximize iron extraction shall inevitably benefit the process of combatting iron deficiency and IDA in India. Moreover, a reason for lack of compliance among Indian households towards iron pots and cooking utensils stem from the tendency of iron to oxidize (rust). However, rusting could be prevented through seasoning of iron utensils with a layer of cooking oil. The extent to which leaching of iron may be affected upon seasoning of iron utensils is yet to be determined. Hence, it is crucial to conduct further investigations that assess the impact of seasoning on the leaching properties of iron utensils.

Food Fortification

Towards reducing the prevalence of iron deficiency and anemia in India, several governmental and non-governmental initiatives have adapted an interventional strategy towards fortification of food with iron. Fortification of staple foods such as wheat flour, rice, and salt have been widely conducted as a cost-effective measure due to their widespread consumption. The government of India has promoted iron fortified rice through social safety net programs such as Integrated Child Development Services (ICDS), PM-POSHAN, and targeted Public Distribution System (PDS). These initiatives sought widespread distribution of rice fortified with ferric pyrophosphate (FPP) and sodium ferric ethylenediaminetetraacetate (NaFe3EDTA) [97]. FPP is an insoluble form of iron, which is micronized to increase its total surface area to maximize absorption, whereas NaFe3EDTA is more water-soluble, which maintains bioavailability in the presence of inhibitors in the diet. In a meta-analysis of 15 studies, a substantial increase in Hb concentration was recorded upon consumption of iron fortified rice, as compared to control groups who consumed unfortified rice [98]. Therefore, iron fortification of rice has been recommended as a population-level intervention to improve the mean hemoglobin levels of countries such as India, where rice is staple, and the population is burdened with a massive prevalence of iron deficiency and anemia.

Wheat and its flour are also staple to the Indian diet, with widespread consumption across parts of northern and western India. In 2018, the Food Safety and Standards Authority of India (FSSAI) mandated set levels, as well as suitable forms of iron fortificants for the fortification of both whole wheat and refined wheat flour in India [99, 100]. Although not mandatory, wheat fortification has gained momentum in India due to the presence and efforts of organizations such as Food Fortification Initiative (FFI), Global Alliance for Improved Nutrition (GAIN), and their partner institutions. NaFe3EDTA has been an effective fortificant of wheat flour due to its ability to inhibit iron-phytate interactions [101]. The use of NaFe3EDTA fortified whole wheat flour as an intervention reported a 67% and 51% reduction in the cases of iron deficiency and IDA, respectively, in iron-deplete primary schoolchildren of both urban and rural India [101].

However, the efficacy of iron fortification may be restricted due to factors including, but not limited to the type of staple food employed as vehicles for iron delivery, the form of iron fortificant utilized, pre-existing conditions leading to iron refractoriness, and processing/cooking technologies employed to prepare iron-fortified foods. Washing and rinsing of fortified rice prior to cooking in order to remove dirt and dust has been shown to decrease its coated iron content [102]. Moreover, the hindering effects of inflammation and infection on iron absorption have been well documented, where an increased production of hepcidin by the liver during such physiological states inhibits the transport of iron into plasma [103]. The prevalence of inflammation and infection are high in tropical regions of the world such as Asia, Africa, and Latin America [104]. In such conditions, iron fortified food as a dietary intervention may not display the intended efficacy in reducing the burden of iron deficiency. In India, infections such as malaria, dengue, typhoid, and tuberculosis are widely prevalent [105]. Yet, studies which have examined the efficacy of iron fortified foods in infection and inflammation-prone populations are lacking in India. Therefore, in order to fully elucidate the effectiveness of interventions through iron fortification, an assessment of both infected and non-infected subjects is essential. Other than inflammation driven by infections, obesity-related inflammation has also been shown to up regulate hepcidin production [106].

By far, ferrous sulfate has been the favored form of iron for fortification, given its water solubility, as well as its similarity to native food iron in terms of its bioavailability and its efficacy in the presence of enhancers/inhibitors [104]. However, iron fortification also leads to undesired sensory changes in food, which varies based upon the form of iron utilized for fortification. This issue remains a primary cause for lack of compliance among consumers and intervention cohorts. These sensory degradations may occur in the form of change in taste and development of odor due to rancidity, as well as change in the color and texture of food. Generally, the most water-soluble and bioavailable forms of iron fortificants tend to confer the highest degree of sensory changes in terms of flavor and color of the food. Less water-soluble forms of iron, such as ferrous fumarate imparts a comparatively lower degree of sensory degradation in food. Hence, the ideal choice of iron fortificant remains a compromise between its solubility, bioavailability, cost, and the acceptability of sensory changes in food [104].

To mitigate the effects of sensory changes, encapsulated forms

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of iron have been developed and tested. In addition to its reduced reactivity within the food matrix such as limited lipid oxidation, it also preserves the bioavailability of iron fortificants. Hydrogenated vegetable oil is the choice of capsule for iron fortificants such as fumarates and sulfates [104]. In recent years, the development of micro-encapsulation and nano-encapsulation technologies has made significant strides towards increasing the bioavailability and promoting controlled release of iron in the gut. Nano-encapsulation of iron in bovine serum albumin (BVA) nanoparticles, used as a fortificant in stirred yoghurt demonstrated stability, while increasing blood count and iron parameters in IDA-induced rats [107]. No adverse effects were noted in the liver, kidney, and spleen. This form of nano-encapsulation also minimized lipid oxidation, while viscosity and water-holding capacity of the food matrix were enhanced, thus increasing the sensorial acceptability of food. The present challenge that stands in the way of widely utilizing this technology is its cost-effectiveness, with current costs soaring roughly three to four times higher than the cost of conventional iron fortification.

Biofortification

Biofortification refers to the development and production of crops with enhanced levels and quality of nutrients in them [108]. It is often employed towards improving the nutrient profile of staple foods in low and middle-income populations as a strategy to improve their nutritional status. Biofortification of crops may be achieved through conventional breeding techniques, genetic engineering of crops, or agronomic fortification through addition of fertilizers. Besides increasing the total concentration of micronutrients in plants, improving overall bioavailability also falls well within the scope of biofortification. When compared to traditional food fortification, biofortification stands out as a significantly sustainable technique due to permanent enhancement to crops, thereby eliminating the need to fortify repeatedly. Apart from its high cost of development, biofortified crops can be grown by farmers without incurring any ongoing costs such as expenses related to additional procurement of fortificants.

Agronomic biofortification is defined as the enhancement of the micronutrient content of plants through the use of fertilizers, which serves as a temporary measure, since the qualities are not passed down to subsequent progenies [108]. Agronimic biofortification is often used to complement other forms of biofortification. A range of rice, wheat, maize, and millet have been successfully biofortified to contain an enhanced iron profile [109]. However, amongst different micronutrients that have been targeted for biofortification, the agronomic approach only works well with zinc, selenium, and iodine, whereas iron is poorly absorbed by plants when added in the form of inorganic fertilizers [110]. This phenomenon has been attributed to the conversion of ferrous iron to its ferric form in the soil, which does not absorb readily into plants.

Biofortification through breeding involves crossing between plants with desirable traits to produce hybrid/segregant progenies that contain agronomical phenotypes of both parents. Parent plant lines featuring desirable traits are selected, following which they are crossed over multiple generations [111]. Repeated back crossing and wide crossing is performed to separate undesirable traits or phenotypes that may have passed down from either parents. An iron-enriched rice variety (IR68144) was developed by crossing semi-dwarf variety (IR8) and Taichung (Native)-1 variety of rice to feature high iron content, high yield, increased disease resistance, and high seed vigor [112]. Moreover, after polishing for 15 minutes, IR68144 retained approximately 80% of its iron, which was significantly higher compared to other red and white pericarp varieties. Additionally, IR68144 rice variety was demonstrated to improve the iron status of non-anemic Filipino women [112].

In recent years, scientific advances in gene editing has promoted the development of genetically modified (GM) crops. The primary advantages of genetic modification over conventional breeding are its efficiency and precision in target gene insertion into plants, the relatively shorter time-frame within which plants with desired traits can be developed as compared to breeding through multiple generations, and the ability to stack multiple genes of interest within a plant to express more than one desirable traits. Iron biofortification through genetic engineering has been achieved in a number of different ways, in a variety of crops [113]. The insertion of “lactoferrin” gene, an iron-binding protein derived from humans, into dehusked rice demonstrated an increase of 120% in its seed iron content [114]. This percentage increase in iron was subsequently deemed suitable for infant supplementation. Ferritin is another gene of interest, primarily due to its capacity for binding 4500 ferric ions per molecule. The transfection of both rice and lettuce with soybean ferritin gene resulted in significantly higher concentrations of iron [113]. Additionally, the co-expression of nicotianamine synthase (*NAS*) gene alongside ferritin conferred a six fold increase in the iron content of rice. Nicotianamine (NA) is a chelator of iron which plays an important role in the uptake, translocation, distribution, and storage of iron in plants [115]. Alternatively, the bioavailability of iron may be improved in crops through dephytinization. Introduction of genes, which synthesize phytase substantially decreased phytate content in rice and wheat [113].

In India, where wheat and rice serve as primary sources of carbohydrates, biofortification of these staple crops could potentially improve national iron status [116, 117]. Between 2017 and 2021, the Indian Council of Agricultural Research (ICAR) developed 28 biofortified wheat cultivars, out of which 15 varieties showcased an increased iron content [118]. Each of these cultivars thrive on very specific soil and climatic conditions, which has led to dispersed cultivation across the different states of India. The efficacy of these crops within the population is yet to be determined. Extensive interventional studies within the Indian population to assess community-wide efficacy of such biofortified crops would provide clearer insights. However, a greater effort towards promoting the penetration of such biofortified crop varieties into the regular diets of a larger segment of the population, as well as encouraging research initiatives towards the development and cultivation of such crops commercially could potentially assist the mitigation of anemia burden in India.

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A major hurdle in the path of crop biofortification in India is the country's reluctance towards the commercial cultivation of GM crops and GMOs for the purpose of food. So far Indian biofortification practices have been limited to agronomic and conventional breeding techniques. Although a variety of GM crops displaying a plethora of desirable traits have been developed and extensively studied, Bacillus thuringiensis(Bt) cotton was the sole GM crop that was approved for widespread cultivation by the Government of India till date. Such abstinence towards commercial cultivation of GM crops, especially for the purpose of food stem from ethical concerns associated with environmental risks such as escape of "engineered" traits into the wild, safety issues pertaining to human health, as well as the welfare of small-scale farmers against market monopoly of large corporations [119]. There also exists ethical dilemmas, where questions relating to the moral implications of altering the "natural" state of a living organism, serve as strong arguments.

The complex regulatory framework governing the development, trials, release, and biosafety of GM crops in India is composed of six committees. Functioning under the "Environmental (Protection) Act 1986" of the "Ministry of Environment, Forest & Climate Change" (MOEFCC), the six committees have been appointed advisory, approval, and monitoring roles (Figure 3). Moreover, the FSSAI maintains stringent regulations pertaining to production, storage, import, distribution, and sale of GM food crops. In 2022, an Indian transgenic herbicide-resistant variety of mustard, "Dhara Mustard Hybrid-11" (DMH-11), gained approval for environmental release by the "Genetic Engineering Appraisal Committee" (GEAC), following which a coalition of environmental and food activists, NGOs, and scientists filed petitions to voice their disapproval of GM crop release in India [120]. Soon after, the Supreme Court of India, on the advice of its "Technical Expert Committee" (TEC) halted the release of DMH-11 due to arising concerns about the potentially higher use of herbicides on such herbicide-tolerant plants, which would ultimately impact the health and well-being of the large mustard consuming population of India [120].

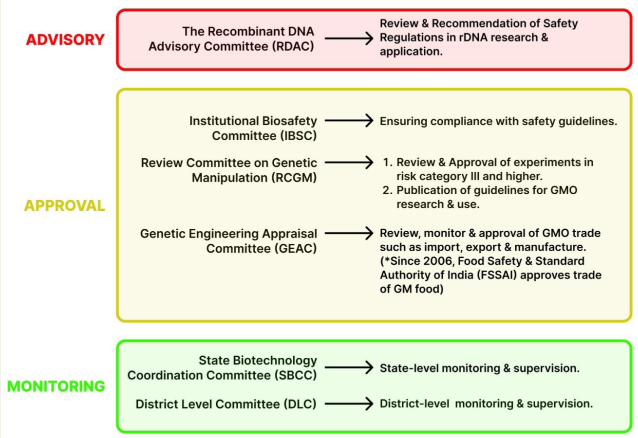

Figure 3: The regulatory framework governing the development and commercialization of Genetically Modified (GM) under the 'Rules 1989' consists of six committees overlooking three different roles, implemented by the Ministry of Environment, Forest & Climate Change (MoEFCC), Department of Biotechnology (DBT), Ministry of Science & Technology, Government of India, and State Governments [129].

The potential in millets: The cultivation of millets has been regarded as one of the most sustainable crop production methods, which require minimal resource input and can be grown in arid soil conditions. Millet's high content of protein, micronutrient, and fiber, as well as its gluten-free property confers health benefits such as improved cardiovascular and gut health, and decreased risk of diabetes mellitus, obesity and cancer [121, 122]. The rising popularity of millets has been attributed to active campaigns and promotions regarding the benefits associated with its cultivation and consumption [123]. The FAO declared the year 2023 as the official 'Year of Millets' with the aim of raising awareness about this crop to agricultural communities across the world. India is the leading producer of millet in the world, making up for roughly 20% of all millets produced globally [124]. According to the "Ministry of Agriculture and Farmers' Welfare", the common varieties of millet produced in India are pearl millet, finger millet, and sorghum. Although there was a decline in millet consumption in India since 1962 through 2010, recent years have witnessed an active interest towards reviving the production and consumption of millets. Moreover, state governments, as well as the central government of India have recently sanctioned financial support to farmers, private industries, and non-profit organizations engaging in millet cultivation. Therefore, this crop provides an exceptional medium to improve the iron status of the Indian population through fortification and biofortification.

Numerous studies have pointed towards the success of iron fortification and biofortification of millets in improving iron status. An increased level of total iron absorption from biofortified pearl millet flour by a factor of "two" was observed among Beninese women [125]. It was noted that a higher phytic acid content in iron biofortified millet did not affect the absorption of the excess iron. In the same study, post-harvest fortification of millets with iron demonstrated an increase in total iron absorption by approximately three folds. Another study on iron-deficient Indian schoolchildren between 12 and 16 years of age reported that iron absorption from iron-biofortified pearl millet meals substantially exceeded the amount of iron absorbed from non-fortified control millet meals [126]. During a period of six months, levels of serum ferritin and total body iron significantly elevated within children with iron deficiency, and increased the likelihood of becoming iron replete by 1.64 times.

Development of "Dhanshakti", the first Indian pearl millet variant with enhanced iron and zinc concentrations began in the early 2000s through 2012, when it was successfully launched in the state of Maharashtra. To tackle nutritional deficiencies among the low-to-middle income Indian population, the ICAR has actively promoted pearl millet biofortification through its "All India Coordinated Research Project on Pearl Millet" (AICRP-Pearl Millet). In 2018, the AICRP-Pearl Millet mandated a minimum requirement of 42 mg/Kg iron concentration in new cultivars of biofortified millet, in order to be qualified for trial approvals and subsequent release. Since then, numerous iron and zinc biofortified varieties of pearl millet have been developed and made available to farmers in India, among which the "AHB 1269 Fe (MH 2185)" hybrid released in 2019 held the highest concentration of iron at 91 mg/Kg [121]. ICAR has also focused on biofortification of finger millets, which often serves as a great source of calcium. In the year 2020 itself, the ICAR released three varieties of high-iron finger millets: VR 929 (131.8 ppm Fe content), CFMV 1 (58 ppm Fe content), and CFMV 2 (39 ppm Fe content) [118].

Conclusion

India faces an array of multifaceted challenges in terms of tackling anemia. A major hurdle remains the inability to diagnose early iron deficiency, the prolongation of which causes IDA. A greater emphasis on both CBC and serum iron parameters would not only promote early detection of iron deficiency, but also the diagnosis of other drivers of anemia. It has also been made evident that diagnostic guidelines based on studies on western ethnic populations may not be wholly representative of the Indian population, especially due to variations in genetic predisposition to clinical conditions, and differing biomarker cutoff values. Therefore, a reevaluation of biomarker cutoffs is recommended to accurately represent the vastly diverse and complex Indian population.

Certain interventional strategies such as dietary diversification and pre-processing/cooking methods could be adapted at a household level to maximize iron intake and its absorption. The majorly plant-based Indian diet presents a high proportion of iron absorption inhibitors, the effects of which could be minimized through household measures. The introduction of educational programs within the large rural population of India could be beneficial towards raising awareness about employable household interventions. Furthermore, fortification and biofortification of a wider range of staple foods could offer a cost-effective avenue for improving the iron status of the nation as a whole. An objective of both the government and concerned authorities should be to facilitate a higher degree of penetration of such fortified/biofortified foods into markets and ultimately into the diets of a wider pool of the population.

It is imperative that further population-based studies be conducted in order to link anemia prevalence to specific dietary trends within different segments of the population. Although, the inhibitory role of tea towards iron absorption has been well documented, it is essential to validate the results within an Indian cohort, which accounts for the role of tea on Indian diets. Moreover, research initiatives towards evaluating the efficacy of fortified and biofortified food within population with high occurrence of infections and inflammation is recommended. A greater emphasis on identifying the population's predisposition to IRIDA would enable formulation of appropriate strategies to combat oral iron refractoriness. Additionally, it is a crucial need of the hour for India to reconsider its stance on GM crop cultivation, given the various advantages associated with its development and cultivation. GM crop cultivation would not only allow efficient biofortification, but also ensure food security for India's ever-growing population.

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