VIEW POINT

Supplementation of higher doses of Iron in programmes to control anaemia is a double edged sword

Preetam B Mahajan[1], Rama Krishna BS[2], Umesh Kapil[3], Balamurugan Ramadass[4]

[1]Associate Professor, Department of Community Medicine, Pondicherry Institute of Medical Sciences; [2]Director, S R M Institutes Gastroenterology, Hepatology, and Transplant (SIGHT) SIMS, Chennai; [3]Professor & Head, Human Nutrition unit, All India Institute of Medical Sciences-New Delhi; [4]Assistant Professor, Department of biochemistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha

Corresponding Author

Address for Correspondence: Dr Balamurugan Ramadass, Assistant Professor, Department of biochemistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha
E Mail ID: balaramadass1@gmail.com

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Introduction

Anemia is a major public health problem globally. Due to loss of 42.2 million disability-adjusted life years (DALYs) in 2011, Iron-deficiency anemia (IDA) was ranked among the top three major causes of disability in the world (1,2). IDA is responsible for at least 50% of anemia and is highly prevalent in India especially among women, children below 5 years, and adolescent girls (3) perhaps due to increased needs, insufficient dietary supplies, poor intervention coverage etc (4). Anemic girls will grow up to anemic mothers and in turn give birth to anemic children. Childhood anemia can have long term consequences. IDA has been associated with developmental deficits, impaired memory and neurodevelopment, diminished physical function, depression, fatigue, loss of vitality, preterm delivery, and lower infant birth weight (5–10). These, effects attributable to anemia remain invisible but are substantial (11), as it has serious health and economic costs and may hinder nation's development. Therefore, effective and safe interventions are urgently needed across the lifecycle. The issue has attracted global attention and for the first time targets have been suggested like reducing the proportion of anemia among women of reproductive age (WRA) by 50% by 2025 in comparison to the baseline year 2011 (12). This is likely to add impetus to global efforts in reducing anemia and monitor the progress towards it.

Iron supplementation (FeS) via age appropriate feeding of elemental iron syrup, tablets or complimentary iron fortified foods is a practical choice often available to policy makers.

The WHO recommendation for settings with high rates of infant and children anaemia include oral iron supplementation that contain approximately 10–12.5 mg/d dose of iron given to infants and children aged 4–23 months (13). It also recommends Micro Nutrient Powders (MNPs) containing ≥12 mg Fe be used in "home fortification" and concluded that the MNPs can be as efficacious as iron supplements. However, Iron Plus initiative covers lifelong supplementation of Iron from the age of 6 month onwards: 1. Bi-weekly 20 mg elemental iron and 100 microgram (mcg) folic acid per ml of liquid formulation and age appropriate de-worming for preschool children of 6-59 months. 2. Weekly supplementation of 45 mg elemental iron and 400 mcg folic acid (WIFS) per child per day for children from 1st to 5th grade in Govt. & Govt. Aided schools, and at AWC for out of school children (6 to 10 years). 3. Weekly dose of 100 mg elemental iron and 500 mcg folic acid with biannual de-worming in adolescents (10–19 years) under WIFS. 4. Weekly

supplementation for women in reproductive age, Pregnant and lactating women. Supplementation for Children 6–60 months as per GoI guidelines: One ml of IFA syrup containing 20 mg of elemental iron and 100 mcg of folic acid biweekly for 100 doses in a year. Iron folic acid supplements be supplied in bottles of 100 ml each and composition, preparation, dose and duration of IFA supplementation will remain same as the existing guidelines (14,15).

Thus, intermittent FeS is being currently practiced across India under the National Iron plus initiative (NIPI) for WRA, children and adolescents, while daily FeS for pregnant and lactating women (16), but the doses recommended under NIPI are slightly higher than the ones suggested by World Health Organisation (WHO) in recently published guidelines (17,18). It is important to understand the consequences of higher doses of FeS and incremental benefit over lower doses as suggested by WHO in reducing the prevalence of IDA.

Excess iron is unlikely to be absorbed in the intestine and is likely to affect the GUT microbiome. At present, there is no clear understanding of its influence on the gut microbiome and improvement of quality of Life. Since Iron is an absolute growth requirement for several species of pathogenic bacteria, it is possible that oral FeS may increase the abundance of pathogenic bacteria in the faeces depending upon how much is absorbed and how much is retained in the lumen of the intestine.

In this paper we have tried to review the effects of excess unabsorbed iron on gut microbiome and indirectly its consequences on health in general, effects of high dose FeS on predisposition to certain chronic diseases, infectious diseases etc. But before that we need to understand the pathway of iron in human body and interplay of factors controlling its metabolism which is elaborated in the subsequent section.

Iron Homeostasis

Fe is an essential trace element, is required for a wide spectrum of biological functions. Iron deficiency leads to inefficient erythropoiesis, increased proportions of hypochromic microcytic Red Blood cells, and depending upon severity of deficiency might result into decreased haemoglobin production.

In Humans, Iron levels are tightly regulated at the level of intestinal absorption as there is no active mechanism for iron efflux. Iron absorption and distribution are tightly monitored, both locally in the intestine, and systemically through hormonal signals. The dietary iron reaching the intestinal lumen is in the ferric state (Fe3+) and is reduced by duodenal cytochrome b reductase and the resulting ferrous iron is then captured by enterocytes, via divalent metal transporter 1, at the apical membrane and is mostly absorbed in the duodenum (19). Intracellular iron may be retained by the enterocytes, or it may enter the bloodstream. Body's iron needs are met by its transfer to the basolateral membrane of enterocytes, from which it is exported via ferroportin and concomitantly oxidized by hephaestin to generate the ferric ion (Fe3+). Fe3+ in the bloodstream is rapidly captured by transferrin, which transports it to all cells in the body. The Fe3+/apotransferrin complex is taken up by all cells, via transferin receptor 1. Intracellular iron is stored in ferritin. In enterocytes, ferritin shells form a molecular barrier between the apical and basolateral membranes of the cells, blocking the movement of iron and preventing it from reaching the basolateral membrane. Once trapped by ferritin, iron is excluded from the rest of the body and is gradually eliminated through the exfoliation of mature enterocytes (20–22). Systemic iron homeostasis is maintained by the hepatic hormone hepcidin, which acts on the blockage of iron recycling from old red blood cells by macrophages (23,24). It has also been suggested that hepcidin decreases iron absorption, by degrading enterocyte ferroportin and/or divalent metal transporter 1. Intracellular iron levels are regulated by iron regulatory proteins (IRPs), which bind to specific mRNA sequences, known as iron-responsive elements (IREs). The IRE/IRP system allows each cell to regulate its iron uptake and iron stores to satisfy its own requirements (25).

Implications of oral Iron supplementation on gut microbiome

The human body plays host to a diverse community of microbes. These resident microbes, approximately 1014 in number, with their nucleic material are collectively described as the human microbiome. Dietary habits greatly influence the composition of the gut microbiome. Maintenance of a healthy human gut microbiome is essential for health.

Oral iron supplementation is recommended and well-studied option to replenish iron stores and therefore is the common way to correct iron deficiency. Excess iron may be extremely toxic to

aerobic organisms because of the formation of reactive oxygen species that can damage nucleic acids and other cellular components. For this reason, iron uptake and cellular iron reserves are tightly regulated in aerobic organisms. Excess iron is tightly bound to transferrin and lactoferrin for safe transportation across the body. Interestingly, human body sequestrates iron to defend itself from most invading pathogens, as they need iron for rapid growth during infection. Less than 10% of ingested iron gets absorbed, while the remaining iron overflows to the colon and is available to the residing microbiota. In Anemic women of reproductive age there was a decrease in the abundance of lactobacillus (26). The fecal iron estimates an inverse relationship with fecal Lactobacilli but has no influence on the abundance of E. coli (27). In childhood, iron supplementation may interfere with the dynamic maturing gut microbiome, which relies on a variety of inter and intra generational factors like maternal nutrition before, during, and immediately after pregnancy, mode of delivery, duration of breast feeding, weaning, and other domestic factors.

In animals, about 12% of iron absorption may occur in the colon. The iron transporters are expressed in the colon of animals and man (28–31), and expression may be increased in iron deficiency states (32,33). In the proximal colon, the absorption of iron and other divalent cations is enhanced by SCFA, which are produced by bacterial fermentation in the colon. Non-digestible disaccharides increased caecal SCFA pools and prevented Fe-deficiency anaemia in gastrectomised rats. Inulin also upregulated mRNA expression for divalent metal transporter1 and ferroportin, and increased faecal levels of Lactobacillus and Bifidobacterium species in pig colon (34–38). Supplementation strategy may be restructured by including probiotics that increase SCFA and help chose between high and low doses of iron for FeS programmes.

Iron supplementation and pregnancy

Iron overload is being viewed as possible risk factor for type 2 diabetes (39,40). Similarly, higher doses of iron supplementation (> 60 mg elemental iron) during pregnancy may be linked with gestational diabetes (41,42). The effects are mediated through lipid peroxidation and/or DNA damage. However, there is lack of evidence about the effect of low dose FeS on gestational diabetes and randomised trials are needed to explore the safety of low dose FeS. Though studies have shown that FeS decreases risk of anemia at term, it is also notable that favourable outcomes in terms of birth weight and risk of preterm labour are achieved at haemoglobin levels between 9.5 and 10.5 g/dl (43). There is an ongoing debate about iron supplementation during pregnancy and increased risk of malarial transmission (44). However, the evidence is conflicting and robust studies are needed to test low dose V/S high dose FeS and risk of malaria during pregnancy.

Other effects of higher doses of Iron

Higher doses of Iron in FeS can increase the risk of enteric and systemic infections (45–48). A study reported increased risk of malaria and higher iron levels during infancy further necessitating generation of evidence linking higher doses of iron in FeS programmes and increased risk of malarial infections during infancy in areas with increased malarial transmission (49). There is growing interest in studies trying to find association between higher doses of Iron used for supplementation during childhood and future risk of early brain aging and neurodegenerative disease outcomes (50,51), though more robust evidence is needed in these areas. High iron levels are known to increase hepcidin levels. Obese individuals have higher hepcidin levels as compared to lean individuals. Whether there is a link between high levels of hepcidin and increased risk of obesity is not yet fully understood (52). Yet another mechanism being investigated is altered GUT microbiota and increased risk of insulin resistance and Obesity (53). Iron supplementation has negative effect on linear growth of iron replete infants and young children (54). Thus, universal FeS can be counter-productive.

In conclusion, though Iron supplementation is effective in controlling anaemia, it is also a pro-oxidative element and can have adverse effects at higher doses. These has been discussed here. However, if these effects can be confirmed by larger and well-controlled studies in local settings it may have huge programmatic implications and guide present supplementation and fortification strategies

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