Gut-Brain Axis Modulation as a Strategy to Address Iron Deficiency Anaemia

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1. Introduction

Iron deficiency anaemia (IDA) continues to persist despite decades of large-scale fortification and supplementation programs. According to global estimates, anemia impacts an estimated 24.8% of the world i.e., about 1.62 billion worldwide (Natekar et al., 2022). The Comprehensive National Nutrition Survey (CNNS) conducted from 2016 to 2018 revealed a high prevalence of iron deficiency anaemia among adolescent girls in India, with 31.3% affected compared to 11.5% of boys (Baruah & Gautam, 2023). Conventional iron supplementation is often constrained by poor fractional absorption and gastrointestinal side effects, and may be further complicated by inflammation-mediated inhibition of iron uptake (Pasricha et al., 2020b). Emerging evidence suggests that iron metabolism cannot be understood in isolation from the gut environment. Microbial ecology, immune signalling, and systemic neuroendocrine regulation appear to form an integrated network governing iron absorption and distribution (Paganini & Zimmermann, 2017). The gut-brain axis, traditionally studied in relation to mood and metabolic health, is increasingly recognised as a regulator of inflammatory tone and nutrient handling (Cryan et al., 2019). This has spurred interest in the gut-brain axis as a potential regulator of iron homeostasis, opening the possibility that targeted modulation of this axis may offer more effective and sustainable strategies to improve iron bioavailability and address anaemia.

2. Understanding Iron Bioavailability

Iron bioavailability refers to the proportion of dietary iron that is absorbed and made available for physiological use. Dietary iron exists in two primary forms: heme iron from animal sources and non-heme iron from plant-based foods and fortified products. Heme iron is more efficiently absorbed, whereas non-heme iron absorption is highly variable and influenced by gastric conditions and dietary inhibitors (Hurrell & Egli, 2010; Pasricha et al., 2020b). Gastric acidity plays a critical role in iron solubility. In the acidic stomach environment, ferric iron (Fe^{3+}) is reduced to the more absorbable ferrous form (Fe^{2+}), facilitating uptake in the duodenum. Reduced gastric acid production whether due to aging, medication use, or gastrointestinal disorders can impair this process (Pasricha et al., 2020b). Absorption occurs primarily in the duodenum via transport proteins such as divalent metal transporter-1 (DMT1). Once internalised, iron is either stored as ferritin or exported through ferroportin, the only known cellular iron exporter. In circulation, iron binds to transferrin and is delivered to tissues, especially the bone marrow for erythropoiesis (Ganz & Nemeth, 2012).

Systemic regulation is governed by hepcidin, the hepatic peptide widely regarded as the master regulator of iron metabolism. Hepcidin binds to ferroportin and induces its degradation, thereby limiting iron export into circulation. Elevated hepcidin reduces iron absorption and promotes sequestration in storage sites, while suppressed hepcidin enhances iron availability (Rishi et al., 2015). Inflammation profoundly alters this regulatory axis. Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), stimulate hepcidin synthesis, leading to reduced iron bioavailability even in the presence of adequate iron stores. This mechanism underlies the anaemia of inflammation, in which iron becomes functionally trapped within storage sites and unavailable for red blood cell production (Ganz & Nemeth, 2012). Together, these mechanisms demonstrate that iron bioavailability is governed not only by intake and absorption but also by tightly coordinated molecular and inflammatory regulatory pathways setting the stage for understanding how microbiota and gut–brain signaling may intersect with iron homeostasis.

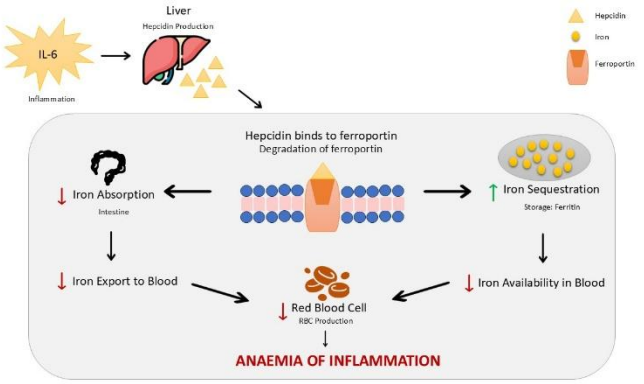

Fig. 1. Inflammation-mediated hepcidin regulation of iron homeostasis leading to anemia of inflammation

3. The Gut-Brain-Iron Interface: An Integrated Regulatory Network

Iron is not only essential for the host, it is equally vital for intestinal microbes. Within the gut lumen, a dynamic competition unfolds between host enterocytes and microbial communities for access to this scarce micronutrient. Many bacteria produce high-affinity iron-chelating molecules known as siderophores, enabling them to sequester iron from the

environment. This competition can directly influence how much dietary iron remains available for absorption (Kortman et al., 2014). Simultaneously, beneficial microbes such as *Bifidobacterium* and *Lactobacillus* can indirectly shape iron bioavailability through metabolic activity, they ferment dietary fibres to produce short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. These metabolites lower luminal pH, enhance iron solubility, and support epithelial integrity. SCFAs also support epithelial integrity and modulate inflammatory tone factors that influence hepcidin signaling and systemic iron regulation (Paganini & Zimmermann, 2017). However, the relationship between iron and the microbiota is bidirectional. Iron supplementation can alter microbial composition, sometimes favoring opportunistic or pathogenic species that thrive in iron-rich environments. Excess luminal iron has been associated with increased gut inflammation and reduced abundance of protective bacteria such as Bifidobacterium, potentially exacerbating dysbiosis (Kortman et al., 2014). Conversely, iron deficiency itself can reshape microbial ecology, further complicating the host microbe balance. Cytokines such as IL-6 directly stimulate hepatic hepcidin synthesis via the JAK–STAT pathway (Nemeth & Ganz, 2009). Increased hepcidin reduces ferroportin expression, limiting iron export into circulation. This provides a mechanistic explanation for why individuals consuming iron-fortified products may still exhibit functional iron deficiency during periods of chronic inflammation or stress. Iron metabolism, therefore, is embedded within a dynamic gut–brain–immune network. Disruption of microbial balance or sustained inflammatory tone may impair iron handling regardless of formulation strength.

4. Translating Mechanisms into Formulation Strategy

If iron bioavailability is modulated by gut microbial ecology, systemic inflammatory status, and neuroendocrine signaling pathways, therapeutic interventions should not be limited to iron supplementation alone but instead incorporate strategies that address these underlying regulatory mechanisms. Targeting the gut-brain axis offers several complementary approaches that may enhance iron handling while minimizing gastrointestinal disruption.

4.1 Prebiotics

Prebiotics are non-digestible dietary substrates that selectively stimulate beneficial gut microbes. Compounds such as inulin, fructooligosaccharides (FOS), and resistant starch enhance the growth of SCFA-producing bacteria, including Bifidobacterium and Lactobacillus species. By increasing SCFA production, prebiotics lower luminal pH, improve iron solubility, and strengthen epithelial barrier integrity. This creates a gut environment more conducive to iron absorption while simultaneously reducing inflammatory signaling. Unlike iron salts, which can disrupt microbial balance, prebiotics aim to optimize the absorptive milieu itself (Christides et al., 2016).

4.2 Probiotics

Probiotics are live microorganisms that confer health benefits when administered in adequate amounts (Apte et al., 2025). In the context of iron metabolism, "iron-friendly" strains are those that:

- Produce SCFAs
- Support epithelial integrity
- Compete with pathogenic bacteria without aggressively sequestering luminal iron

Certain strains of *Bifidobacterium* and *Lactobacillus* have demonstrated potential to improve iron absorption indirectly by modulating gut pH and inflammatory tone. By stabilizing microbial ecology, probiotics may reduce hepcidin-inducing inflammation and promote more efficient ferroportin-mediated iron export.

4.3 Synbiotics

Synbiotics combine prebiotics and probiotics into a synergistic formulation. This approach simultaneously introduces beneficial microbes while providing the substrates needed for their growth and metabolic activity. By enhancing colonization and SCFA production, synbiotics may amplify both chemical (improved iron solubility) and immunological (reduced inflammation) mechanisms. Such combined strategies may prove particularly valuable in populations where conventional iron supplementation alone produces limited response or significant gastrointestinal side effects (Zakrzewska et al., 2022).

4.4 Postbiotics and Psychobiotics: Emerging Frontiers

Beyond live bacteria, postbiotics which are bioactive microbial metabolites or cell components, are gaining attention. SCFAs themselves can be considered functional postbiotic mediators that influence epithelial health and immune regulation without requiring viable organisms. Even more intriguing is the emerging field of psychobiotics, defined as microbial interventions that confer mental health benefits through gut-brain axis modulation. By influencing vagal signaling, stress responses, and inflammatory pathways, psychobiotics may indirectly improve iron handling through neuroendocrine regulation. Reduced stress-associated cortisol release and attenuated cytokine production could help normalize hepcidin levels and optimize iron absorption. Together, these therapeutic strategies shift the paradigm from iron replacement to environmental modulation, targeting microbial composition, inflammatory balance, and gut-brain communication to improve systemic iron status.

5. Evidence from Preclinical and Clinical Studies

Preclinical models demonstrate that in animal models of iron deficiency, supplementation with prebiotics such as inulin and resistant starch has been associated with increased SCFA production, improved intestinal morphology, and

enhanced iron absorption (Husmann et al., 2022). Clinical evidence, while still emerging, is encouraging. Human trials evaluating probiotic and synbiotic supplementation have demonstrated modest but significant increases in serum ferritin and haemoglobin, particularly in individuals with mild iron deficiency. For example, administration of Lactobacillus plantarum 299v alongside iron has been shown to enhance iron absorption in women of reproductive age (Hoppe et al., 2015). Such findings suggest that microbial co-administration may improve iron uptake, potentially through luminal acidification, improved epithelial function, or reduced microbial competition. Importantly, microbiota-targeted interventions have also been linked to reductions in inflammatory markers such as IL-6 and C-reactive protein (CRP). Given the central role of inflammation-driven hepcidin in functional iron deficiency, these findings provide mechanistic plausibility for improved systemic iron availability through immune modulation (Nemeth & Ganz, 2022). Although variability exists across populations, the collective evidence supports a translational hypothesis: optimising gut microbial ecology and gut-brain signalling may improve iron status through restoration of regulatory balance in inflammatory and neuroendocrine pathways.

6. Challenges and Considerations

Although modulation of the gut-brain-microbiota axis represents a promising strategy to enhance iron bioavailability, several critical challenges must be addressed prior to its broad clinical implementation and translation into practice.

6.1 Microbial Competition for Iron

Iron is a limited resource within the intestinal lumen, and both host and microbes actively compete for it. Many bacteria produce high-affinity siderophores to sequester iron, potentially reducing its availability for host absorption. In some contexts, enhancing microbial growth without careful strain selection could paradoxically divert iron away from the host rather than improve bioavailability. This highlights the need for precise targeting of beneficial, non-competitive strains.

6.2 Risk of Pathogenic Overgrowth

Iron supplementation itself has been associated with shifts in microbial composition that may favor opportunistic or pathogenic species. Increased luminal iron can promote the expansion of enteric pathogens that thrive in iron-rich environments, potentially increasing gut inflammation. Any strategy that modifies iron availability must therefore consider ecological balance within the microbiome.

6.3 Individual Microbiome Variability

The human microbiome is highly individualized, shaped by diet, geography, early-life exposures, and genetics. As a result, responses to prebiotics, probiotics, or synbiotics may vary significantly between individuals. A formulation that enhances iron absorption in one population may have minimal or different effects in another, complicating universal recommendations.

6.4 Need for Personalized Nutrition

These interindividual differences point toward a need for personalized or precision-based approaches. Tailoring interventions based on microbial composition, inflammatory status, and baseline iron parameters may improve efficacy and reduce unintended consequences. Future strategies may involve microbiome profiling to identify individuals most likely to benefit from specific microbial or psychobiotic interventions.

6.5 Regulatory and Standardization Limitations

Finally, regulatory frameworks for probiotics, synbiotics, and postbiotics vary globally and often lack the rigor applied to pharmaceutical interventions. Strain specificity, dosing consistency, and long-term safety data remain areas requiring further standardization. Without clear regulatory pathways and high-quality clinical trials, translation into mainstream anaemia management will remain limited.

7. Conclusion

Iron deficiency has long been framed as a problem of insufficient intake, addressed primarily through supplementation and fortification. Yet emerging evidence across microbiology, immunology, and neuroendocrinology suggests a more complex reality: iron bioavailability is shaped not only by diet, but by microbial ecology, inflammatory tone, and bidirectional gut-brain signaling. From microbial metabolites that enhance iron solubility, to cytokine-driven hepcidin regulation, to stress-mediated neuroendocrine effects on absorption, iron homeostasis appears deeply embedded within systemic physiological networks. Efforts such as the Human Microbiome Project have reinforced the concept that host-microbe interactions are central to metabolic regulation, providing a framework for rethinking nutrient deficiencies through a systems biology lens. Addressing iron deficiency, therefore, may require moving beyond simple supplementation toward restoring regulatory balance. Modulating the gut-brain axis, through microbiome-targeted, anti-inflammatory, and neuroendocrine-informed strategies which offers a paradigm shift from replacement therapy to physiological optimization. In doing so, we move closer to treating anaemia not merely as a nutritional deficit, but as a disorder of integrated biological regulation.

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