Improving Iron Bioavailability with Prebiotic Galacto-oligosaccharides

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Key messages

> Nearly half of all children under five years, mostly living in Africa and Asia, suffer from anemia.
> One of the predominant factors contributing to this bleak outlook is iron deficiency.
> It is difficult to meet the iron needs of older infants and young children through local diet alone.
> Recent trials question the safety of MNPs containing a dose of 12.5 mg iron per sachet, particularly in areas with high malaria endemicity.
> New studies show that prebiotics can improve iron absorption and reduce the negative side effects of iron supplements in infants with iron deficiency.

Iron deficiency anemia is a global concern

Nearly half of all children under five years, mostly living in Africa and Asia, suffer from anemia (Figure 1). These children will likely fail to reach their full cognitive, motor, and social-emotional potential, will probably fail at school, fail to achieve their income potential, and remain trapped in the poverty cycle. One of the predominant factors contributing to this bleak outlook is iron deficiency. In fact, according to the World Health Organization (WHO), iron deficiency is among the 10 most serious risks in countries with high infant mortality rates.

Children aged 6–23 months, with their increased iron requirement due to rapid growth, are recognized as being at a higher risk for iron deficiency anemia. While the iron stores received at birth are sufficient to support normal functions and growth for the first six months, it is difficult to meet the needs of older infants and young children through local diet alone, particularly in resource-poor countries. Inclusion of fortified complementary foods or supplements can help this age group meet the additional iron requirements of approximately 4 mg per day or more. It is imperative to have effective strategies in place for ensuring adequate iron nutrition and reducing anemia during these formative years.

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Strategies to ensure iron adequacy

Strategies to ensure adequate iron nutrition and/or to treat anemia include a combination of measures tuned to the specific situation and circumstances. First, breastfeeding should be promoted and supported. Other measures include promotion of dietary diversity, fortification of staples and complementary foods, and iron supplementation for groups at high risk or with especially high needs. Multiple micronutrient powders (MNPs) have been adopted as an approach for providing micronutrients to populations where needs are highest and other interventions are difficult to implement, such as in Africa and Asia.

For infants and young children aged 6–23 months, WHO recommends point-of-use fortification of complementary foods with iron-containing MNPs to improve iron status and reduce anemia. Current MNPs contain a dose of 12.5 mg iron per sachet, equivalent to the dose provided by oral iron supplements for the treatment of iron deficiency anemia in infancy. This high dose is to account for the potential inhibitory substances...
in complementary foods and high plasma hepcidin concentrations due to infections. Recent trials, however, question the safety of these MNPs, particularly in areas with high malaria endemicity. Most of the iron from these MNPs passes unabsorbed into the infant colon, where it can promote the growth of enteropathogens and increase the risk of diarrhea, particularly in poor hygienic conditions. In a trial with Kenyan infants, MNPs increased the Enterobacteriaceae:Bifidobacteriaceae ratio, numbers of enteropathogenic Escherichia coli, gut inflammation, and diarrhea. Alternatives to lower the iron dose in MNPs while maximizing iron absorption and ensuring suitability for 6–24-month-old children are thus warranted.

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Prebiotics – a novel approach to increase the iron bioavailability from MNPs

Prebiotics are substrates that are selectively utilized by host microorganisms, conferring a health benefit. Galacto-oligosaccharides (GOS) are an example of a prebiotic, and consist of soluble carbohydrates structured as chains of galactose with a glucose end-piece with varying chain length (Figure 2). They are enzymatically produced from lactose and may have increased selectivity toward Bifidobacterium spp. compared with the effect of some other prebiotics.

Also known as “colonic food,” GOS resist digestion by gastric acid and pancreatic enzymes in vivo and are preferentially fermented by the beneficial intestinal bacteria. Fermentation results in the production of short-chain fatty acids (SCFAs) that decrease luminal pH, which may in turn reduce growth of enteropathogens. This favorable effect was recently demonstrated by Paganini et al. in a study with Kenyan infants.

Several human studies have reported the positive influence of GOS on bacterial communities in the gut and in improving calcium absorption. However, evidence on the direct contribution of GOS-induced changes in microbiota to absorption of iron has only recently been demonstrated by Prof. Michael
Zimmerman’s group at ETH\textsuperscript{8,10} Paganini et al.\textsuperscript{10} reported substantially higher iron absorption from an MNP with 5 mg iron and 7.5 g GOS in 6–14-month-old Kenyan children than previously described for MNPs containing 12.5 mg iron (18.8\% vs. 4–9\%). The authors estimate that the amount of iron absorbed from the new MNP would cover the total iron need of 0.69 mg/d in 6–12-month-old infants.\textsuperscript{10} In another randomized 4-month trial with Kenyan infants, a reduction in anemia was noted with the new MNP formulation containing a low dose of highly bioavailable iron. Moreover, the provision of 7.5 g GOS in this new MNP mitigated the adverse effects of iron on the gut microbiome, resulting in greater abundances of Bifidobacterium and Lactobacillus, lower abundances of virulence and toxin genes of pathogens, less enterocyte damage, and a lower incidence of treated respiratory tract infections.\textsuperscript{8} According to Prof. Michael Zimmerman, “These are the first human studies that clearly show that prebiotics can improve iron absorption and reduce the negative side effects of iron supplements in infants with iron deficiency.”

Mechanisms that may explain the increase in iron absorption with GOS include:\textsuperscript{8,10,22}
\begin{enumerate}
\item Lowering of luminal pH, thereby improving iron solubility;
\item Creation of an environment in the colon that promotes the reduction of Fe(III) to Fe(II);
\item SCFAs stimulating the proliferation of epithelial cells, thereby increasing absorptive surface area of the colon;
\item Increased expression of genes involved in iron absorption;
\item Anti-inflammatory effects in the colon, reducing circulating hepcidin.
\end{enumerate}
It is also relevant to note that the studies by Paganini et al. were in mostly iron-deficient anemic infants, whereas previous studies were in non-anemic adults. In animals, anemia sharply increases colonic iron absorption, and this absorptive pathway may also become important in anemic humans. Also, infants have a gut ecosystem that differs from that of adults, including higher abundances of Bifidobacteria and lower colonic pH. It is plausible that potential prebiotic-induced changes in colonic iron absorption may be stronger in infants.

“New evidence suggests that prebiotic GOS offer opportunities to more effectively combat iron deficiency in vulnerable populations”

In conclusion
New evidence suggests that the prebiotic GOS can improve iron bioavailability as well as reduce the potential adverse effects of iron fortification on the infant gut. This offers opportunities to effectively and safely combat iron deficiency in vulnerable populations.

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