Editorial

See corresponding article on page 1020.

Tackling iron deficiency in infants: galacto-oligosaccharides may be up to the task

Fudi Wang

Beijing Advanced Innovation Center for Food Nutrition and Human Health, China Agricultural University, Beijing, China; and School of Public Health, School of Medicine, Zhejiang University, Hangzhou, China

Iron, an essential trace element, plays a critical role in maintaining health by mediating mitochondrial function and DNA synthesis and repair and serving as a critical factor for key enzymes (1). In children, iron deficiency is the most common nutritional deficiency. In particular, iron deficiency is highly prevalent among resource-limited nations in Africa, in which two-thirds of all preschool-aged children are estimated to be anemic and one-half of their anemia is caused by iron deficiency (2). In contrast, iron deficiency is much less prevalent in resource-rich countries such as the United States, although the incidence is highest among infants and young children because of their high iron requirements during development (2).

Iron deficiency in early childhood causes developmental delays and poor physical performance, and dietary iron supplementation and food fortification are commonly recommended in many countries to increase iron intake and correct or prevent iron deficiency and anemia. In Africa, iron-containing micronutrient powders (MNPs) are widely used to control anemia in infants. However, although these MNPs contain high amounts of iron (providing 12.5 mg Fe/d), they have limited iron absorption (only 4–9%) and they can increase the risk of enteropathogenesis, diarrhea, or both (3). Therefore, iron-containing MNP formulations for infants must be improved to increase iron absorption and to minimize the occurrence of adverse effects.

In current years, a growing body of evidence suggests that prebiotics—a nondigestible food ingredient that has beneficial effects on the gut microbiome and the host's health—can be used as a dietary supplement to enhance the absorption of minerals such as iron, zinc, and magnesium (4, 5). In this issue of the Journal, Paganini et al. (6) report that infants who consume dietary iron supplements together with prebiotic galacto-oligosaccharides (GOSs) have significantly increased iron absorption compared with a control group. In their study, 50 infants in Kenya were fed a maize porridge fortified daily with an MNP containing 2.5 mg ferrous fumarate and 2.5 mg sodium iron EDTA (NaFeEDTA). One group ($n = 22$) received the iron-containing MNP together with 7.5 g GOSs/d (Fe+GOS group), whereas the other group ($n = 28$) received the iron-containing MNP without GOSs (control group). After 3 wk of this dietary intervention, iron absorption, blood iron markers, and gut bacteria were measured in both groups. The results showed that the infants in the Fe+GOS group had higher iron absorption and iron bioavailability than the control group. Consistent with this finding, the iron storage biomarker ferritin and the iron-regulatory hormone hepcidin also increased in the Fe+GOS group. A recent report by the same group showed that the inclusion of GOSs in an iron-containing MNP can mitigate the adverse effects of iron on the gut microbiome in infants in Kenya (7). Together with the current report, these findings indicate that giving infants GOSs with an iron-containing MNP can help improve the efficacy of iron supplementation while reducing the risk of adverse effects associated with high iron intake.

In the intestine, the uptake of dietary iron is mediated by the divalent metal transporter 1 (DMT1), whereas the movement of iron from the intestinal epithelium to the blood is mediated by the "iron gate" protein ferroportin. Ferroportin can interact with the liver-derived iron-regulatory hormone hepcidin and is degraded when dietary iron uptake, body iron stores, or both are sufficient. The presence of an infection can stimulate the secretion of hepcidin, which reduces intestinal iron uptake and decreases iron availability. Therefore, on the basis of the so-called hepcidin-ferroportin axis, several compounds such as Caulis Spatholobi, black soybean seed coat extract, myricetin, and vitamin C have been shown to regulate hepcidin concentrations to increase dietary iron absorption from the intestine and to increase the mobility of iron from iron-storing organs (8). For example, black soybean seed coat extract has been shown to downregulate hepcidin, thereby improving iron status in mice (9). Although compounds that target the hepcidin-ferroportin axis are promising, evidence in humans, particularly infants, is scarce.

The availability of iron in dietary supplements can be affected by many factors, including the form of iron, the presence of infection, and the gut microbiome. Nevertheless, the efficacy of prebiotics in improving iron absorption provides new possibilities for future iron supplementation strategies. Iron supplements that contain prebiotics

Supported by grants from the National Natural Science Foundation of China (31530034 and 31330036; to FW).

Address correspondence to FW (e-mail: fwang@zju.edu.cn).

Abbreviations used: DMT1, divalent metal transporter 1; GOS, galacto-oligosaccharide; MNP, micronutrient powder; NaFeEDTA, sodium iron EDTA.

First published online September 6, 2017; doi: https://doi.org/10.3945/ajcn.117.165878.

have several advantages over conventional iron supplements. First, prebiotics increase the absorption of iron from both iron supplements and regular iron-containing foods. Second, reduced doses of iron can be used in iron-containing MNPs that include prebiotics without reducing efficacy in infants (10). Finally, prebiotics may also increase the absorption of other minerals, such as zinc, magnesium, and calcium, which may be beneficial in terms of iron absorption and other essential minerals (4, 5). Despite these advantages, however, the long-term effects of combining prebiotics with an iron supplement require further study, ideally in large cohorts of infants and other vulnerable populations such as adolescents and pregnant women.

It is also interesting to note that based on their C-reactive protein concentrations, the infants in studies by Paganini et al. had iron deficiency but no obvious sign of infection or inflammation (6, 7). Thus, the efficacy of GOSs should be tested in iron-deficient subjects with infectious disease or an inflammatory condition. This is particularly relevant given that in anemia of chronic disease, inflammation can induce hepcidin overexpression, which increases iron retention in iron-storage organs and reduces ferroportin in the small intestine, potentially reducing the efficacy of iron supplementation.

Prebiotics selectively fermented by gut bifidobacteria and the subsequent production of short-chain fatty acids can decrease the pH in the colon, which may increase the solubility of minerals (5). Interestingly, Paganini et al. (6) found that the consumption of prebiotic GOSs increased the fecal amounts of *Bifidobacterium* spp., *Lactobacillus*, *Pediococcus*, and *Leuconostoc* spp. and reduced fecal pH. In addition, low intestinal pH due to GOSs may also facilitate the dissolution of ferrous fumarate. Moreover, prebiotics have been reported to increase the expression of intestinal DMT1 and ferroportin while decreasing the expression of intestinal IL-6, IL-10, and TNF-α in rats (10). Although the underlying molecular mechanism by which prebiotics increase iron absorption remains to be determined, Paganini et al. provide compelling evidence to support the notion that combining GOSs with a supplement containing ferrous fumarate and NaFeEDTA is an effective—and potentially safer—strategy for iron-deficient infants. On the basis of these promising findings, future studies are clearly needed to evaluate the long-term effects of this formula in a larger cohort of infants and to test the feasibility and efficacy of including prebiotics in iron supplements in a broader population with iron deficiency anemia.

The author declared no competing financial interests.

REFERENCES

1. Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. Cell 2017;168:344–61.
2. WHO. The global prevalence of anaemia in 2011. Geneva (Switzerland): World Health Organization; 2015.
3. Tondeur MC, Schauer CS, Christofides AL, Asante KP, Newton S, Serfass RE, Zlotkin SH. Determination of iron absorption from intrinsically labeled microencapsulated ferrous fumarate (sprinkles) in infants with different iron and hematologic status by using a dual-stable-isotope method. Am J Clin Nutr 2004;80:1436–44.
4. Coudray C, Bellanger J, Castiglia-Delavaud C, Rémésy C, Vermorel M, Rayssignuier Y. Effect of soluble or partly soluble dietary fibres supplementation on absorption and balance of calcium, magnesium, iron and zinc in healthy young men. Eur J Clin Nutr 1997;51:375–80.
5. Laparra JM, Díez-Municio M, Herrero M, Moreno FJ. Structural differences of prebiotic oligosaccharides influence their capability to enhance iron absorption in deficient rats. Food Funct 2014;5:2430–7.
6. Paganini D, Uyoga MA, Cercamondi CI, Moretti D, Mwasi E, Schwab C, Bechtler S, Mutuku FM, Galetti V, Lacroix C, et al. Consumption of galacto-oligosaccharides increases iron absorption from a micronutrient powder containing ferrous fumarate and sodium iron EDTA: a stable-isotope study in Kenyan infants. Am J Clin Nutr 2017;106:1020–31.
7. Paganini D, Uyoga MA, Kortman GAM, Cercamondi CI, Moretti D, Barth-Jaeggi T, Schwab C, Boekhorst J, Timmerman HM, Lacroix C, et al. Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: a randomised controlled study in Kenyan infants. Gut 2017 Aug 3 (Epub ahead of print; DOI: 10.1136/gutjnl-2017-314593).
8. Imam MU, Zhang S, Ma J, Wang H, Wang F. Antioxidants mediate both iron homeostasis and oxidative stress. Nutrients 2017;9:671.
9. Mu M, Wu A, An P, Du X, Wu Q, Shen X, Wang F. Black soyabean seed coat extract regulates iron metabolism by inhibiting the expression of hepcidin. Br J Nutr 2014;111:1181–9.
10. Marciano R, Santamarina AB, de Santana AA, de Lima Correia Silva M, Amancio OMS, da Penha Oller do Nascimento CM, Oyama LM, de Morais MB. Effects of prebiotic supplementation on the expression of proteins regulating iron absorption in anaemic growing rats. Br J Nutr 2015;113:901–8.