

WHAT'S NEW IN IRON SUPPLEMENTATION: YOUR PATIENT'S GUT MAY THANK YOU

Anna Augustin, DO

Family physicians commonly encounter patients with iron deficiency throughout their daily practice. This should come as no surprise, as iron deficiency is the most common global nutritional deficit and affects over 1 billion people in the world. If untreated, deficiency can lead to fatigue, shortness of breath, mental fog, and anemia. These symptoms can affect a patient's wellness and productivity and can eventually lead to lifelong chronic illness.

Who is at risk?

Even without clinical signs of anemia, iron deficiency can still have a negative impact on an individual. Iron plays an essential role in cognitive development, immune function, viable gestation, and normal growth. With these important considerations in mind, it is no surprise that the highest groups at risk for iron deficiency are young children and pregnant women. Consuming iron fortified foods or supplementing products with iron is considered the first line of deficiency treatment and prevention. In industrialized parts of the world, education and dietary coaching may be an adequate first line of therapy. In resource limited areas, however, increasing iron intake through diet alone is not feasible and the mainstay of treatment is oral supplementation.

What about oral supplements?

Oral iron is recommended for both iron deficiency anemia patients as well as groups at high risk for iron depletion that cannot supplement this element through diet alone. However, the side effects of oral iron supplementation can deter patients from adhering to a typical once-daily treatment plan. These side effects include nausea, vomiting, constipation, diarrhea, and dark stools. In patients requiring increased dosages, these side effects become exponentially more severe and treatment adherence rates are low. Fortunately, some new studies have emerged that may make treatment of this common condition more tolerable to both the patient and their GI tract.

FOODS TO INCREASE IRON ABSORPTION

- Meats: Chicken, beef, seafood
- Vitamin C: fruits, juices
- Green vegetables: spinach, broccoli, etc.
- Fermented foods: sauerkraut, kimchi

DIETARY FACTORS THAT DECREASE IRON ABSORPTION

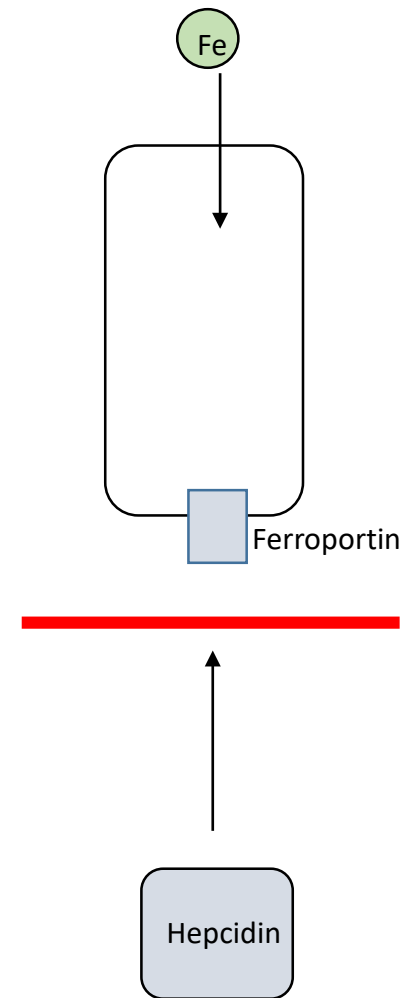
- Calcium: milks and yogurts
- Tannins: coffee, tea, chocolate
- Phytates: Nonfortified cereals, highly processed flour
- Prolonged cooking

What have we learned about iron absorption?

To understand the treatment of iron deficiency, a basic review of iron absorption is crucial to family physicians. Iron, in the reduced form, is absorbed across the enterocyte cell membranes of the duodenal and early jejunal epithelial cell surfaces. It is then transferred across the basal cell membrane into the systemic circulation by a protein known as ferroportin. The regulation of the amount of iron introduced into the systemic circulation is dependent on a peptide called hepcidin. Hepcidin, the “iron regulator hormone,” is a peptide produced by the liver in response to an increase in systemic iron concentrations. If iron is ingested in excess, hepcidin levels also increase and inhibit any further transport of iron by acting on ferroportin. If an individual is iron deficient, hepcidin levels fall and iron is readily transported across the upper GI epithelial membrane cells. Hepcidin has a half-life of about 24 hours and can markedly limit the amount of iron available to the systemic circulation while levels are high.

How has hepcidin affected iron supplementation?

With the discovery of hepcidin’s long half-life, the utility of daily or multi-dosing regimens may not necessarily coincide with underlying iron physiology. In line with prior guidelines, most iron deficient individuals are placed on 60 mg of iron daily (in children, 2 mg/kg) for a duration of at least three months. Some patients are even placed on twice daily dosing regimens. With these high levels of increased iron intake, hepcidin levels increase with each dosing. As hepcidin increases, the total amount of iron absorbed becomes minimal while the adverse gastrointestinal side effects of oral iron remain constant. It is no surprise that patients placed on these high dose regimens often discontinue treatment due to adverse effects. Ultimately, treatment adherence rates fall with increased oral supplementation.



IRON DEFICIENCY



Dietary modification

Increase ascorbic acid

Avoid phytates/tannins

**DIETARY
MODIFICATION
FAILED**



**Begin oral iron
supplementation**

What has new research shown?

New research has indeed confirmed that after patients take an oral iron supplement, hepcidin levels increase and impair absorption of the subsequent next daily dose. With the newly understood physiology of hepcidin in mind, recent trials have started to compare daily dosing to alternate day iron supplementation. Although the studies have been small, they have shown that total iron absorption is equivocal when comparing daily and alternate day dosing. Alternate day iron supplementation has been shown to be as efficacious as a daily dosing regimen. These pilot studies have opened a new frontier in research opportunities involving the most common nutritional deficiency affecting our world.

What is the bottom line?

As physicians, awareness of an alternative to traditional iron supplementation can help us connect with our patients on many levels. Patients can feel overwhelmed at times when taking multiple pills, and alternate-day dosing can help alleviate any anxiety about medication burden an individual may have. Additionally, it can help lower medication cost by halving the required dosing amount for uncomplicated iron deficiency. Although not yet proven in studies, alternate day dosing can theoretically lower gastrointestinal side effects and increase treatment compliance rates. For patients struggling with unwanted treatment side effects, a new alternative can offer a patient some needed reprieve regarding side effect profiles. In discussing viable treatment alternatives and addressing patient concerns, the family doctor can foster a greater physician-patient relationship and bolster patient compliance to a needed treatment plan.

While more research is needed to implement a new standard of care, the first few studies on iron supplementation and hepcidin have had promising results. As family physicians, this new research can lead to a positive discussion between patient and provider. It can also give us an alternative to offer if patients simply cannot stick to the standard dosing regimen. In regards to our own education, it offers physicians a new insight into a decades-old condition. With the ever changing world of research, it shows us how continued questioning can positively contribute to our understanding of disease. Most importantly, it gives us a reason to stay current on the latest research: our patients will ultimately reap the benefits.

**INTOLERABLE
GI SYMPTOMS**



**Lower to minimum dosing
requirement**

**Take supplement at
bedtime**

**Take supplement with
meals**

**SIDE EFFECTS
THREATENING ADHERENCE**



**Consider alternate day
dosing**

References

1. World Health Organization. (2001.) *Iron Deficiency Anemia. Assessment, Prevention and Control*.
2. Camaschella, C. (2019). Iron deficiency. *Blood*, 133(1), 30-39. Accessed August 12, 2019. <https://doi.org/10.1182/blood-2018-05-815944>.
3. Lindsay H. Allen, Iron Supplements: Scientific Issues Concerning Efficacy and Implications for Research and Programs, *The Journal of Nutrition*, Volume 132, Issue 4, April 2002, Pages 813S–819S, <https://doi.org/10.1093/jn/132.4.813S>
4. Ganz, T. (2011). Heparidin and iron regulation, 10 years later. *Blood*, 117(17),4425-4433. Accessed August 13, 2019. <https://doi.org/10.1182/blood-2011-01-258467>
5. Stoffel, N. U., Cercamondi, C. I., Brittenham, G., Zeder, C., Geurts-Moespot BSc, A. J., Swinkels, D. W., ... Zimmermann, M. B. (2017, October 9). Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Retrieved from <https://www.sciencedirect.com/science/article/abs/pii/S2352302617301825>
6. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood*. 2015;126:1981–9.
7. Schrier SL, Auerbach M. Treatment of iron deficiency in adults. Wolters Kluwer: UpToDate; 2017.
8. Miller J. L. (2013). Iron deficiency anemia: a common and curable disease. *Cold Spring Harbor perspectives in medicine*, 3(7), 10.1101/cshperspect.a011866 a011866. doi:10.1101/cshperspect.a011866