

Iron deficiency anemia - Section 11

Novel approaches to oral iron treatment

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Take home messages

- Oral iron supplements are an important and accessible method to treat iron deficiency and iron deficiency anemia, but have low bioavailability and may cause side effects.
- Daily supplementation regimens are associated with an increase in hepcidin concentration, and with decreased absorption.
- Alternate day, low dose schedules provide higher fractional absorption compared to daily schedules. As side effects are likely dose dependent, such schedules may result in higher compliance and efficacy.
- However, reducing and spacing doses may reduce the total iron absorbed, despite increased fractional absorption.

Introduction

It is estimated that iron deficiency anemia (IDA) affects >1 billion people worldwide¹ and the prevalence of iron deficiency (ID) is likely higher. ID and IDA remain prevalent nutritional deficiencies also in countries with developed infrastructure and service industries. In Europe, ID and IDA were estimated to affect 10 to 32% and 2 to 5% of women of reproductive age, respectively.² Deficiency develops when physiological requirements and losses cannot be met by the iron absorbed from the diet.³ Requirements are increased in young children, adolescents and women of reproductive age, due to growth and menstrual losses, and in women, choice of contraceptive method has been associated with iron status, likely due to its effect on menstrual bleeding.⁴ Dietary iron absorption is determined by the balance of heme and non heme iron, as well as absorption enhancers (ie, ascorbic acid) and inhibitors (ie, tannins, phytates) which can substantially affect overall iron bioavailability⁵ (Table 1). Pathological conditions substantially contribute to the burden of IDA. These can either increase losses (such as hemorrhage, GI lesions, hookworm infestation, blood donation, anti-inflammatory drugs) or decrease absorption (inflammatory conditions, enteropathy, achlorhydria).⁶ Thus, it is of central importance for effective

and long lasting treatment to assess, understand and treat the underlying causes for ID.⁷

Current state of the art

Iron absorption in the GI tract is governed by systemic and local stimuli acting in concert. Systemically, hepcidin binds to ferroportin, the only known cellular iron exporter, modulating systemic iron release from enterocytes. Hepcidin is regulated by iron status, erythropoietic stimuli and hypoxia as well as infection and inflammation. The cell itself governs its iron metabolism with iron responsive proteins (IRP), which directly sense cytoplasmic iron concentrations and consequently bind to iron responsive elements (IRE) within the mRNA of key iron proteins and transcriptional factors (such as transferrin receptor, dimetal transporter 1, ferritin, ferroportin, hypoxia inducible factor-2). Enterocyte iron absorption is also regulated by oxygen partial pressure via the hypoxia inducible factor-2 (HIF2 α). Enterocyte cellular iron metabolism has been linked to the “mucosal block”, which describes the inability of the mucosa to absorb additional iron following an iron bolus.⁸

Diagnosis of uncomplicated iron deficiency is straightforward,⁶ but it is challenging in presence of comorbidities such as infections or inflammation. A comprehensive review has been recently published on this topic and is recommended as further reading.⁹

Oral iron supplementation remains the primary therapy for ID and IDA, and guidelines generally foresee the use of 100 to 200 mg elemental Fe/day either as single or as split dose. It has long been known that iron absorption from supplements is generally low and individually variable. When supplements are given with foods, fractional absorption varied between 0.5 and 13% from a 50mg dose, in contrast to the fasting state, which showed absorption ranges between 1.2 and 28%, depending on the subject's iron status.¹⁰

The authors report no conflicts of interest.

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Table 1**Dietary iron bioavailability in dependence of dietary composition.²⁰**

	Dietary iron bioavailability			
	5%	10%	12%	15%
Dietary characteristics	Very little meat/fish, limited ascorbic acid source foods, diet rich in tannins/polyphenols, and phytic acid (low resource settings)	Regular meat/fish intake and regular intake of ascorbic acid source foods (daily). Diet with moderate intake in phytic acid rich cereals and legumes foods and some tannins/polyphenols.	Moderate meat/fish intake and moderate intake of ascorbic acid source foods (every meal). With limited phytic acid source foods and no coffee or tea within 2 hours of the main meals	High meat/fish intake, a high intake of ascorbic acid with meals, a low intake of phytate-rich cereals, and no coffee or tea within 2 hours of the main meals
Iron requirement ¹ (iron intake) in young women (>18 yr), mg	58.8	29.4	24.5	19.6

RNI=Recommended Nutrient Intake, designed to cover the requirements of 97.5% of the population.

It is also well known that iron supplements cause gastrointestinal side effects^{*11,12} which are likely connected to gastric/duodenal irritation by the soluble iron salts administered (nausea, epigastric pain, constipation, heartburn, diarrhea). Such side effects are prevalent (22–31% of subjects reporting any side effect) and in an early study investigating ferrous sulfate, -gluconate or -fumarate against placebo, were not influenced by the iron compound used.¹³ There are suggestions, mostly from observational studies, that “slow release” formulations may cause less side effects than conventional formulations,^{*12} but this observation was not confirmed in a recent meta-analysis including only randomized, double blind studies.^{*11} Generally, it is plausible that lower dosages cause less side effects,^{*6,14} even if the current evidence in this regard is insufficient.^{*11}

As hepcidin is directly responsive to the serum iron level and the percent of transferrin saturation (%TS), it was expected that an iron supplement would acutely increase %TS and elicit an increase in serum hepcidin,¹⁵ furthermore, hepcidin has a circadian rhythm, increasing during the day.¹⁶ Recent studies using common iron supplement dosages of 60 to 240 mg elemental Fe in form of FeSO₄, have showed to increase Hepcidin for more than 24 hours. This elevation was found to be associated with the decrease (35–45%) in fractional iron absorption on the day following the first administration.^{*17} Furthermore, the 6-fold increase in iron dose (40–240 mg Fe) corresponded only to a 3-fold increase in iron absorbed (6.7–18.1 mg).¹⁷ These effects were first identified in female subjects with depleted iron status (serum ferritin <20 µg/l) without anemia, and were then confirmed in a subsequent study comparing a 14 day daily with a 28 bi-daily intervention.^{*18} Splitting dosages during the day did not result in a clear increase in iron bioavailability, suggesting limited, if any, benefit for this practice in terms of fractional absorption.^{*18} A follow up study was conducted with blood donors with mild anemia, and confirmed the findings after 24 hours from the first supplement administration, with a decrease in fractional absorption of ≈40%. After 48 hours from the second administration, in anemic subjects, no residual inhibition of iron absorption was detected. Interestingly, also serum concentration of hepcidin returned to baseline levels. The lack of residual absorption inhibition in concomitance with a “normal” hepcidin value suggest the absence of a mucosal block 48 hours post administration in this patient group with mild anemia.¹⁹

Overall these findings suggest that low dose, and alternate day schedules result in higher fractional absorption (ie, increased absorption efficiency). As it is likely that side effects occur on a dose dependent manner, reducing the dose and implementing alternate day schedules may result in less side effects while maintaining high bioavailability. However, it is important to note that decreasing the dose will generally also decrease the total amount of iron absorbed, as the gain in

efficiency does not fully compensate for the lower levels of iron administered.

Future perspectives

As treatment with oral iron is likely to remain the most accessible treatment for uncomplicated ID and IDA, it is important that high quality data on GI side effects from different supplementation schedules is generated. Ideally, treatment should be personalized, and the supplementation schedule (dose, frequency) should take into account the severity of the deficiency, individual oral supplements tolerability, and should also include advice on how to prevent relapse to iron depletion once the therapy is completed (dietary advice).

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