

GlobiFer® Newsletter August 2018

Iron: what should we keep in mind?

Let's get back to basics...

In healthy food, there are two kinds of natural iron: haem iron and non-haem iron:

- Haem iron is found in meat, poultry, seafood etc. It comes from **animal proteins** in our food. Haem iron consists of iron in ferrous state (Fe^{2+}), nested in the haem core of the haemoglobin and myoglobin.
- By contrast, non-haem iron, is found in **vegetable-based food** or from other sources like **water**. The iron is in a less soluble form, the ferric state (Fe^{3+}).

When dietary intake is not enough to sustain the iron requirement for an individual, the iron status is unpaired.

To cope with this unintended status, 2 solutions are available:

- **oral iron supplements** are a first and most frequently used solution and are prescribed as drugs or available as food supplements on the market. Iron can be available in elemental form, Ferrous, Ferric, in haem iron or trapped in larger complexes. All those formulations have proven their effectiveness in correcting the low iron levels or the anaemia (iron deficiency).
- **iron infusion**: it is a procedure in which iron is delivered to the body intravenously and can only take place in hospitals or haemodialysis centers where healthcare providers can monitor the procedure and react immediately in case of possible adverse reactions. The IV iron infusion gives the fastest results as it delivers the whole required dose immediately in the bloodstream. It is only used in specific circumstances and/or pathologies.

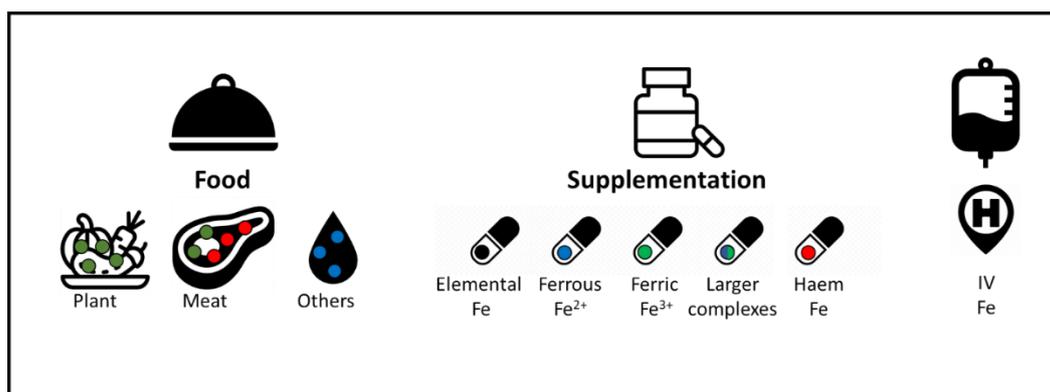


Figure 1: Different forms of iron

GlobiFer® is one of the oral alternatives on the market.

- It contains **fortified haem iron**: Ferrous salt is fortifying the haem iron which is derived from bovine haemoglobin. This unique formulation results in better absorption since it is well known that both iron forms influence each other and lead to an increase in absorption of 40%^{1,2,5}.

In this section we will only concentrate on the oral route, which is the preferred route of administration by patients and physicians because of its ease and convenience.

The absorption of iron

The absorption pathway⁴ and efficacy of iron depends on its specific form. It is well known that body iron content is controlled largely through iron absorption rather than iron excretion.

The first step that facilitates absorption is getting it soluble and therefore bioavailable (figure 2).

Increasing solubility to increase bioavailability has been the key point in research and development. Some researchers have developed new technologies to deliver higher amount of iron in the bloodstream (iron complexes, ect...). Other simply investigated an increase in iron salt concentration to increase the bioavailability. On the other side, GlobiFer Intl. has developed a unique formulation based on one of the natural forms of iron in the body: iron linked to the haem part of haemoglobin fortified by iron sulphate.

- Which formulation is more soluble?

Haem iron, Ferrous iron and larger complexes of iron are known to be more soluble than Ferric iron forms (figure 2: in the stomach, inset 1). The less soluble form of iron is the elemental iron. All iron formulations are designed to release iron in the stomach and/or the upper part of the duodenum, except large complexes of iron which are stable in the stomach and have been developed to be released in the intestine. As mentioned before, the more iron is soluble the most readily it will be absorbed.

- What happens in the stomach?

In the stomach (inset 1), acidity is the only parameter influencing the conversion between the different iron forms (elemental, ferric, ferrous) and therefore impacting the solubility. Interestingly, the solubility of haem iron is reported not to be influenced by acidity, so haem iron is stable in the stomach, resulting in less stomach distress (see reason explained below)⁴.

- What happens in the intestine?

In the intestine (figure 2 inset 2), dietary enhancers and inhibitors may influence ferric and ferrous iron absorption by the intestinal cells (Inset 2). Absorption of those iron forms is strongly dependent on the diet. Some types of food can inhibit the absorption of iron, and for that reason most of the ferric and ferrous iron preparations contain a higher iron concentration to balance this inhibition. This might of course lower the tolerability.

Interestingly, multiple studies report only one known absorption inhibitor identified for haem iron: calcium. At this stage, one may conclude that haem offers advantages leading to greater amount of available iron ready to be absorbed at the surface of intestinal cell by receptors even at low concentration (inset 3).

Because iron sulphate and haem iron are present in GlobiFer[®] formulations, one may argue that absorption takes place through salt iron and haem iron gates in the intestinal cell wall. GlobiFer[®] contains both types of iron and makes use of both entrances working independently.

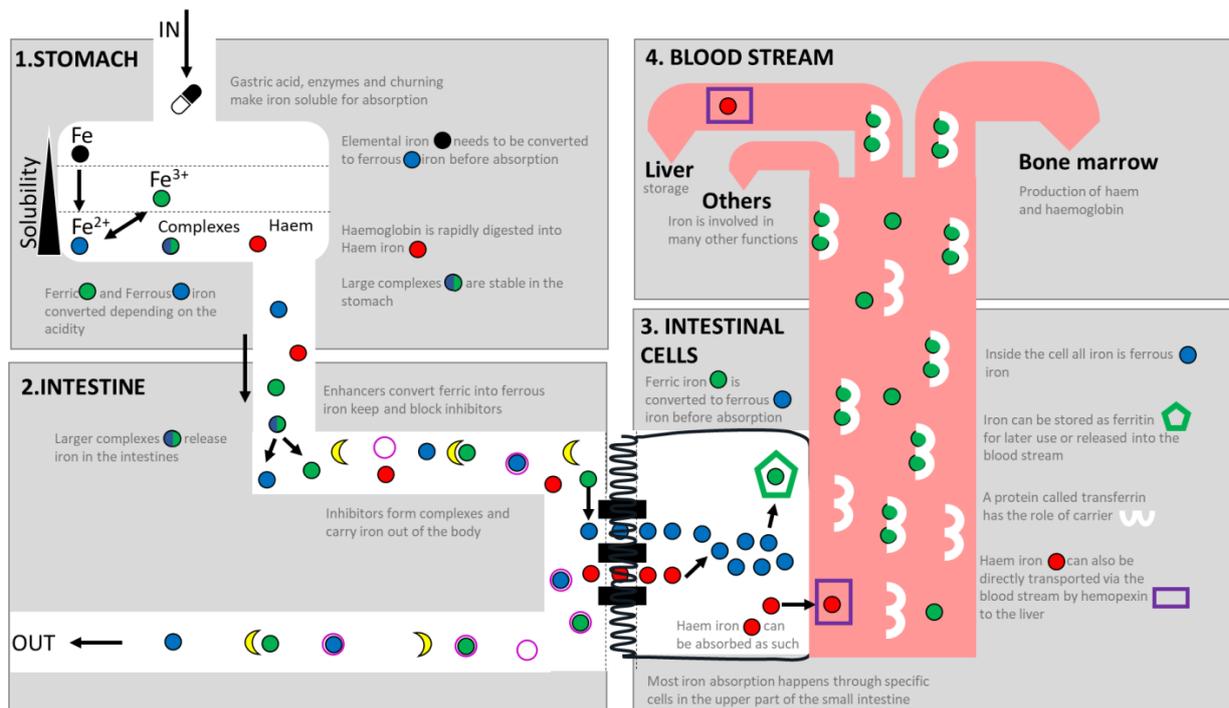


Figure 2: Iron Absorption scheme



- What about the tolerability and side effects?

It is known that iron, both in ferrous (II) and ferric (III) oxidation states, can interfere with oxidative reactions and produce the highly toxic hydroxyl radical leading to GI distress with clinical manifestation such as nausea, vomiting or constipation, ect.... Increasing their concentration to improve the bioavailability does lead to increased risk of those side effects⁸.

The haem group of the haemoglobin in GlobiFer[®] offers a shield to protect the mucosae from those reactions. Nevertheless, one may question the tolerability of the haem group. Indeed, studies have reported that the haem ring can also penetrate lipid membranes and participate in the oxidative reactions which make it a potent catalyst of injury.

However, this has been contradicted by other findings: in the cell a mechanism of protection has been developed to avoid that. Haem is rapidly catabolized by haem oxygenase (HO) (that opens the porphyrin ring producing biliverdin and carbon monoxide) which releases iron that can quickly be bound by ferritin (inset 3). This mechanism of protection allows rapid shifting of the iron from the haem into the ferritin core where it is less available to catalyse deleterious reactions. Besides this above-mentioned mechanism of protection, another protein, hemopexin, has been identified as direct transporter of haem in the plasma to specific sites of catabolism (liver) thus also preventing potential oxidative stress through the release of free iron. Other than scavenging haem, the haem-hemopexin complex has also been shown in animal models to be able to activate signalling pathways promoting iron storage, cell survival and modulation of gene expression of protein involved in the absorption of iron^{6,7}.

Critical role of iron in bacterial infection

It is well known that iron have a noticeable effect on human health acting as catalyst in living cell metabolism. Iron has also numerous and diverse functions in bacterial cells such as cell composition, metabolism, enzyme activity and host cell interaction which include pathogenicity³. Therefore, strategy of increasing the iron concentration to increase the bioavailability may lead to a risk of exacerbation of some types of bacterial infection. Because of the low iron concentration of GlobiFer[®], iron cannot be used by most bacteria and consequently their growth is not stimulated. The latter can be of interest while individuals have bacterial infections and are in need of iron supplementation.

It is valuable to present GlobiFer[®] to physicians and pharmacist based on the physiology of its absorption and not only based on the lower side effect profile reported after its use. The latter is indeed an important argument to bring to physicians mainly when discussing the impact of side effect on the compliance.

However, the physiology of absorption of fortified haem iron takes advantage of the iron metabolism itself and are worthen to present to physicians and healthcare providers.

The combination of haem iron and ferrous iron leads to:

- Better solubility in the stomach bypassing the influences of acidity
- Low influence of diet/food on the solubility and consequently on the bioavailability
- Two independent gates to enter intestinal cells
- Two pathways for iron transport in the blood: ferritin and/or hemopexin. Hemopexin being a short cut to reach the catabolism site, the liver.
- Low iron concentration in ferrous salt form to avoid overload of the intestinal cells and reducing the risk of GI distress.

References:

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