Ferritin

1. Clinical trials referenced for bioavailability and side effects

STUDIES SHOWING BIOAVAILABILITY LESS THAN SULFATE

(Szikne et al. 1997)

Compared 5mg of Ferritin (from bovine spleen) and Sulfate in 10 people.

"In 10 subjects, geometric mean absorption from 5mg of ferritin iron was 3.8% when taken without and 3.2% when taken with food (P > 0.05). These values were significantly lower than absorption from the same dose of iron given as ferrous sulphate, which averaged 24.1% without and 8.2% with food."

My summary

The results imply that sulfate is about 6 times more bioavailable than ferritin when taken without food. I don’t really understand how the labeling worked, but this is what (Kalgaonkar and Lönnerdal 2008) says while mentioning this study and comparing it to others: "It is likely that the disparity among these studies was due to the labeling techniques used. For example, conventional extrinsic labeling is not likely to result in exchange of the isotope and Fe within the insoluble mineral core, while intrinsic labeling may not be valid as various methods have been used to induce ferritin (inflammation, antibody-coating of erythrocytes, etc) from animal sources and Fe in this type of ferritin may not be representative of that inside ‘native’ ferritin"

STUDIES SHOWING BIOAVAILABILITY SAME AS SULFATE

(Theil et al. 2012)

A study that compared ferritin against ferrous sulfate and hemoglobin iron at various strengths. 73 woman, not anemic and each group had a similar iron status. Supplements taken after overnight fast and no solid food consumed for 3-4 hours after. Iron was labeled and usual tests done 14 days after supplements ingestion.

Quite a confusing setup, made possible with the two sets of radio labeling. Doses of 0.5 mg elemental iron as ferritin tested against sulfate from 0.5mg - 49.5mg, Fe as hemoglobin from 0.5mg - 49.5mg. Also some of the sulfate and Hb supplements were GR (gastric resistant), and some of the sulfate had ascorbic.

Results:

Because the increase of sulfate and heme iron from 0.5 to 9.5 didn’t affect ferritin, they say it agrees with other studies about there being a separate pathway to absorption with ferritin, separate from both heme and non-heme pathway.

"We found that ferritin is a slow release source of iron, readily available to humans or animals"
side effects

Only thing mentioned is this: "Compared to chelated nonheme iron (Fe-NTA), ferritin iron is a natural, slow release iron source. The slow iron release properties of ferritin iron described here could protect intestinal cells from oxidative damage caused by some conventional iron supplements"

My summary

Low dose of ferritin used as it was looking at dietary levels rather than supplement levels. They didn’t discuss the bioavailability of ferritin in relation to sulfate directly as the study was focused on pathways, but looking at their results it seems like sulfate and ferritin have about the same bioavailability? Maybe.

(Davila-Hicks, Theil, and Lönnerdal 2004)

This study compared ferritin (both from plant and animal) against ferrous sulfate. 15 non-anemic women were given either animal ferritin or sulfate, and another 15 were given either plant ferritin or sulfate. All iron was radio labeled. They consumed their supplement of 1mg Fe with a breakfast (contained inhibitors), but then refrained from eating for 4 hours. Usual measurements taken at 14 and 28 days as well as full body counting at start and end.

results

" Iron was used equally well from both types of ferritin and from ferrous sulfate: 22% from plant-type ferritin (high phosphate:iron) compared with 17% from ferrous sulfate and 21% from animal-type ferritin (low phosphate:iron) compared with 22% from ferrous sulfate. This study provided evidence that iron was absorbed equally well from animal ferritin and that the type of mineral (animal or plant) does not affect iron absorption from ferritin." Study indicated a differing path of absorption for ferritin compared to sulfate. No mention of side effects.
My summary
Supplements were given with food, but they say they had a low content of inhibitors. The ferritin they used was quite messed around with so it could be labeled. But they seem to show that the ferritin whether from plant or animal had the same bioavailability as sulfate.

(Fochi, Ciampini, and Ceccarelli 1985)
Compared Ferritin with sulfate in 69 pregnant women. They were divided into four groups and usual tests taken after 30 and 60 days. Groups I'm interested in are group II - 80mg equivalent ferritin
group III - sulfate 105mg
Looks like it was just as effective as sulfate even though slightly less iron. No mention on what kind of ferritin used

"From Figures 7 and 8 it appears that the comparison between the cases treated with ferritin (alone or associated) and those treated with ferrous sulphate allows the following considerations: 1) red cell count is initially greater in the group treated with ferrous sulphate, but after 50 days of treatment it is not significantly different; 2) haemoglobin concentration, initially greater in the group treated with ferrous sulphate, after 50 days of treatment increases in the group which was administered ferritin; 3) corpuscular value, initially greater in the group treated with ferritin, becomes similar in the two groups after 50 days of treatment; 4) iron, initially not different in the two groups, after 30 days and- more significantly- after 50 days is greater in the group treated with ferritin."

side effects
"In our investigation, the frequency and severity of the side-effects induced by the treatment have not been a problem. All the preparations used have been well tolerated, except for two cases of intolerance due to ferrous sulphate."

My summary
Might take a little longer to kick in than sulfate, but appears to be as effective. Not clear what type of ferritin used. Ferritin slightly better tolerated but not sure if it’s significant.

(Łonnerdal et al. 2006)

Study of 16 women. Iron taken with a meal (bagel, cream-cheese and apple juice). Given equivalent iron (2.5mg) in either soybean ferritin or ferrous sulfate form. They weren’t anemic. Used reconstituted ferritin which had 480 iron atoms/protein molecule.

Results

Iron was well absorbed from soybean ferritin and from ferrous sulfate (means of 30% and 34%, respectively) with no significant difference between groups.

"Although iron absorption from soybean ferritin, as determined by whole-body counting (29.9%), was somewhat higher than that from horse spleen ferritin in our previous study (21.9%) (15), it should be noted that iron absorption from FeSO4 also was proportionally higher (34.3% compared with 16.7%). This finding is most likely explained by the smaller amount of iron given in the present study, because the difficulty in isolating large amounts of purified soy-bean ferritin, in contrast with ferritin from the unusually iron-rich horse spleen, restricted the amounts of purified soybean ferritin available and we had to limit the dose of iron given. It is well known that iron absorption is inversely correlated with the dose given and with iron status (26-28)."

My summary

Study showed there was no significant difference between the bioavailability between sulfate and ferritin. Small dose and taken with food inhibitors. No mention of side effects.

Other Studies of Interest

(Hoppler et al. 2008)

This was a study that was investigating the amount of ferritin that survives cooking of various legumes. Not totally relevant but makes some interesting observations about bioavailability studies of ferritin.

"For ferritin-iron, contradictory results have been published from several human studies, either showing good (13–16) or poor (17–21) iron absorption from ferritin. These differences have been associated with isotopic labeling of ferritin-iron. It has been suggested that labeling of
animal ferritin under inflammatory conditions, as employed in the studies showing poor iron bioavailability, may have led to a ferritin molecule that releases iron less readily [9]. Recently, it was proposed that ferritin is resistant to digestion in the gastrointestinal tract and that it might even be absorbed intact by the mucosal cell [14]. Such a mechanism would protect ferritin-iron from interactions with iron absorption inhibitors, like phytic acid or polyphenols, which are largely responsible for the low bioavailability of iron from plant sources [22,23].

(Lönnerdal 2009)

Good article, it summarises a lot of other studies. Similar to (Hoppler et al. 2008), it states that a lot of earlier studies on ferritin need to be taken with caution due to their measurement methods (extrinsic labeling).

2. Info and sources regarding inhibitors and enhancers

(Theil et al. 2012) - Study outlined in section above.

"Ferritin iron is absorbed by a different mechanism than iron salts/chelates or heme iron. Recognition of a second, nonheme iron absorption process, ferritin endocytosis, emphasizes the need for more mechanistic studies on ferritin iron absorption and highlights the potential of ferritin present in foods such as legumes to contribute to solutions for global iron deficiency"

Non-GR capsules (covered with the enteric polymer) releases the contents in the stomach, whereas GR capsules release the contents in the intestine.

![Graph showing iron bioavailability comparison between Non-GR and GR capsules](image)

My summary

Ferritin seems to be absorbed by a pathway separate from both Heme and the usual non-heme pathway. Not much known about it. Ascorbic seems to hinder absorption when it is released in the stomach (guessing because ascorbic speeds up the release of the Fe from the protein). Ascorbic helps in the intestines though, due to assisting in turning the ferric into ferrous iron so it can be absorbed. Implies that ascorbic acid shouldn’t be taken with it unless it’s a slow release version.

(Kalgaonkar and Lönnerdal 2008)

Used the caco-2 cell method to compare the effects of inhibitors and enhancers on Fe from animal ferritin and from sulfate. All inhibitors did as expected and inhibited sulfate. In contrast only tannins had an effect (positive) on Fe uptake from undigested Ferritin, or
digestion when the ph was high, But digested ferritin was effected in the same way as sulfate. Because they tested the effects of digestion at two different ph levels, they found that at the lower ph (more acid) level, more Fe was released from the Ferritin core and then treated like normal ferric iron.

"These results suggest that Fe uptake occurs from both undigested as well as digested Ft but, possibly, via different mechanisms."

"This suggests that with increasing severity of digestion conditions, Fe may be released from the mineralized core and may subsequently be made available for interactions with common dietary factors following its release."

My summary

Again indicating a separate pathway for ferritin absorption. So one pathway is where it goes through digestion whole and gets absorbed intact. Another is where the ferric iron gets released from the protein and then gets absorbed along the usual path. How much of the ferritin goes along each path depends on factors like gastric acid and stomach acidity.

(Lönnerdal 2009)

Same view as expressed above in (Kalgaonkar and Lönnerdal 2008), just expands on pathways. "The extent to which these 2 mechanisms is used is likely determined by individual factors, eg, meal size, diet composition, and age."

(Hoppler et al. 2008)

Not really relevant but interesting. As mentioned above this was a study that was investigating the amount of ferritin that survives cooking of various legumes. Although food like beans has quite a lot of ferritin, we probably don’t absorb a lot of it intact. Cooking plus the ascorbic and polyphenols liberate most the Fe.


These guys are resellers of ferritin so take with caution. But they do list a couple of additional studies and provide quite a lot of information on ferritin. Main gist is that it’s fairly well absorbed but slow release/takes a while to work. Very well tolerated with low side effects. They say ascorbic helps absorption, but no evidence given of this.
3. General info references

(Lönnerdal 2009)
ferritin is what we and virtually all living organisms use to store iron. It has an ‘iron core’ of up to 4500 Fe(III) iron molecules inside an organic protein shell.

(Knovich et al. 2009)
"Ferritin structure: apoferritin forms a roughly spherical container within which ferric iron is stored as a ferrihydrite mineral. Apoferritin refers to the iron-free form of the protein; the iron-containing form is termed holoferritin or simply ferritin."

(Lönnerdal 2009)
"Many legumes and cereals, eg, soybeans, lentils, beans, peas, and corn, contain ferritin. These plant ferritins, which are similar to animal ferritins, are large proteins with molecular weights of ’450,000 and consist of smaller subunits with molecular weights of ’28,000 (29). Ferric iron is found as an “iron core” inside a shell of ferritin subunits complexed with oxygen and phosphate and is insoluble.

"At current concentrations of ferritin, a 50-g meal of soybeans provides only 0.5 mg of iron, which is a small amount compared with the daily iron requirements."

"When isolated from commercially available legumes, each ferritin molecule contains 800–1000 iron atoms"

-This study showed that 49% of the iron in soybeans was bound to ferritin whereas the remainder was bound mostly to phytate.

(Lönnerdal 2010)
Legumes such as soybeans, peas, lentils, and beans contain a plant form of ferritin (“phytoferritin”) which is similar to ferritin found in iron stores in humans and other animals [51–54].
My interpretation of all these studies

Ferritin really needs to be intrinsically labeled for accurate bioavailability measurements. This is quite difficult though and requires a lot of messing around with the ferritin. There is the possibility that the ferritin used in these tests isn’t representative of ‘normal’ ferritin however it seems that this is still better to go by than intrinsic labeling. It seems that ferritin is about as bioavailable as sulfate. The more Fe that gets released from the ferritin during digestion, the less bioavailable it seems to be. This seems to be affected by gastric acid and stomach ph.

Very little information about side effects, just one study mentioned no side effects. It would make sense that it would have less side-effects as natural ferritin doesn’t seem to have side effects, and it’s a ferric form of iron which tend to have less side effects than ferrous. Also it’s naturally slow release. Reviews from health sites seem to say it has less side effects. hardly scientific but all i’ve got to go on. I’d put it at around the ferric level of side effects but with a lot of uncertainty.

4. References used in this section


