Heme Iron peptide (HIP)

1. Clinical trials referenced for bioavailability and side effects

STUDIES SHOWING BIOAVAILABILITY MORE THAN SULFATE

(Seligman, Moore, and Schleicher 2000)
Study compared Japanese HIP (from pig hemoglobin) with ferrous fumarate and a placebo. Used the serum iron method in 14 non-anemic patients, where it was and taken with food (all the usual inhibitors). 20mg dose.

results
"Using our formula obtained from Ekenved’s data to calculate iron absorption (19), the amount of iron absorbed for those taking 20 mg of iron as HIP was at least 2.0 mg whereas <1 mg was absorbed from 20 mg iron as ferrous fumarate.”
"Thus our studies indicate that iron present in HIP, similar to hemoglobin, when taken with a meal, allowed for significantly increased iron absorption using 20 mg of iron which, based on US RDA and RDI recommendations, is recommended for those at risk for iron deficiency"

This study is referenced in (Nagaraju et al. 2013) as "HIP increased serum iron levels 23 times greater than ferrous fumarate on a milligram-per- milligram basis"

My summary
So the HIP was a lot more effective against fumarate that had been taken with food. Small sample, different type of HIP to what is now available, and the serum iron test is not a great test as can be seen by the decrease in both the placebo and sulfate result from 3 to 6 hours. They suggest this could be down to the known diurnal change in serum iron, which is one of the reasons this test is unreliable. Labeling HIP is hard though and this still gives some indication of its bioavailability. Says it showed similar results of HIP as Hemoglobin results.
(Proulx and Reddy 2006)
Used Caco-2 cell systems measuring ferritin. Compared Hemoglobin from soy and bovine against sulfate. Bovine Hb was about double the bioavailability of sulfate.

My summary
The RBV of BHb is about twice that of sulfate when tested in the Caco-2 cell method, which has been shown to be quite a good approximation of human absorption. Measured BHb not HIP though, but HIP is often compared to BHb so can be used as an approximation.

(Tang, Chen, and Zhuang 2014)
Not ideal as it's a study on rats not humans, but including due to lack of studies. Comparing the positive control (sulfate) with the moderate dose (same amount as HIP), it appears that HIP had double the absorption of sulfate. HIP from bovine hemoglobin.

"Higher Fe bioavailability and fewer side effects were observed when compared with FeSO4, moreover, in vivo antioxidant activity was also observed that enhanced the activities of antioxidant enzymes and reduced malondialdehyde levels in IDA rats. Therefore, heme iron enriched peptide obtained from bovine hemoglobin might be exploited as a safe, efficient new iron supplement."

my summary
In rats HIP is about twice as effective as sulfate. They say less side effects but not much details. And it was on rats.
(Ekman and Reizenstein 1993)
A study of 27 women given a supplement that had both Sulfate (16mg) and Fe from bovine Hb (2mg). The iron was labeled and the relative absorption of each was calculated. Supplement was given with meal with all the inhibitors.

Table 2. Mean values, standard deviations, and range values for the absorption rates

<table>
<thead>
<tr>
<th></th>
<th>Normal (%) ± s.d.</th>
<th>Iron deficiency (%) ± s.d.</th>
<th>Total (%) ± s.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous group</td>
<td>4.59 ± 3.4 (1.0 - 12.4)</td>
<td>9.45 ± 7.8 (0 - 22.9)</td>
<td>6.83 ± 6.4 (0 - 22.9)</td>
</tr>
<tr>
<td>Heme-iron group</td>
<td>16.13 ± 8.0** (8.0 - 33.7)</td>
<td>22.03 ± 8.9* (9.7 - 35.5)</td>
<td>19.08 ± 9.0** (8.0 - 35.5)</td>
</tr>
</tbody>
</table>

*p < 0.05, ** p < 0.01 between ferrous and heme iron groups

My summary
Heme iron was absorbed about 3 times as much despite the 1/8 dose. Not sure how the heme used in the study compares to HIP available now. Also keep in mind that it was given with inhibitors of sulfate. As they noted "However, if a meal had been given containing no inhibitors of the absorption of ionizable iron, but instead promoters like ascorbic acid, the advantage of heme iron would have been reduced."

(Nagaraju et al. 2013)
A study done on 40 kidney disease patients (not on dialysis). They were given either 11 mg of HIP orally 3 times per day, or 200mg iron sucrose through IV once a month. Trial lasted 6 months.

Table 2 Change in Hgb, ferritin and TSAT from baseline to 6 months by treatment group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIP baseline</th>
<th>HIP 6 m</th>
<th>p-value</th>
<th>IV iron sucrose baseline</th>
<th>IV iron sucrose 6 m</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>110.5 (104-119)</td>
<td>117 (110-128.8)</td>
<td>0.15</td>
<td>108.5 (102-117)</td>
<td>113 (107.5-120.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Ferritin</td>
<td>71 (40-143)</td>
<td>85.5 (44-104)</td>
<td>0.81</td>
<td>67 (27-100)</td>
<td>244 (71.5-298)</td>
<td>0.003</td>
</tr>
<tr>
<td>TSAT</td>
<td>17 (14-20)</td>
<td>21.5 (17-29)</td>
<td>0.05</td>
<td>16.5 (10-20)</td>
<td>21.5 (17-27)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Not much difference in Hb or TSAT (transferrin saturation), however the ferritin increased more in the IV group.

Side effects:
The gastrointestinal adverse events were not greater in the HIP group than the IV iron sucrose group.

My summary
Hard to compare as the doses were different. Maybe about 3x as much iron in the HIP as the IV iron sucrose. Also need to keep in mind that they were kidney disease patients. Still, HIP managed to improve the Hb as much as the IV treatment, but the ferritin result was a lot higher in the IV group which is the key indicator. So less effective than IV iron sucrose but hard to say how much less considering it raised Hb just as well. Similar low side effects.
(Nissenson et al. 2003)
A 6 month study on hemodialysis patients comparing HIP with IV iron. Similar results to (Nagaraju et al. 2013), when they switched to HIP, they initially dropped TSAT but then it reversed to show no significant difference with IV. There was a significant reduction in serum ferritin levels though.

My summary
Again hard to compare, but seems to be a good treatment for dialysis patients who tend to have a high ferritin but still lacking iron.

OTHER/ INCONCLUSIVE

(Tae-Sik Nam 2006)
56 people, supplement taken with food, compared japanese HIP, korean HIP and iron salt. No labeling of iron and used the Serum iron method which isn’t the most accurate especially for relatively small doses (12mg elemental iron used).

results
"In summary, the absorption of iron in HIP is far more efficient than iron salt. It also appears that the solubility of HIP is critical for absorption since iron uptake from water soluble HIPk is far greater than water insoluble Hlj. Moreover, our results indicate that heme-iron absorption is regulated by iron status through a heme receptor, whereas iron-salt absorption is unregulated."

My summary
It showed that different types of HIP can have a widely different result on absorption. Solubility is important for absorption. Taken with food, HIP was more effective than ferrous aminoacetate - some kind of iron salt i don’t know anything about. No mention of the food so could well have inhibitors. Also not the most accurate method.

(Barraclough et al. 2012)
62 patients of chronic kidney disease were given either Proferrin (a HIP) or slow-release ferrous sulphate. No advantage with HIP. It actually reduced Ferritin levels. Not representative of normal population though. One thing to note though, these patients were give supplements on empty stomach. Other studies took them with food. Need a study comparing both on empty stomach with normal population. Also note that FS was slow release.

side effects
no better for HIP. Side effects in total, however just looking at gastrointestinal side effects: HIP - 22%, Sulfate slow release - 13%

"Given that this study was not powered adequately to explore differences in gastrointestinal toxicity between the two preparations, no definitive conclusions can be drawn from these data. However, they do suggest that a major improvement in gastrointestinal symptomatology with HIP therapy would be unlikely, even in a larger study population."
“Compared to iron(II)sulphate, which is selected as a reference and whose bioavailability is set at 100 by definition, the bioavailability of lactoferrin scales from 100 to 800, the one of haemoglobin from 100 to 700, the ones of iron gluconate and iron phosphate are 89 and 25, respectively.” (Hurrell 1997) is referenced for this but I found no mention of these figures.

Proferrin data sheet
Proferrin® Forte is a unique product for dietary management of iron deficiency. Excellent GI tolerability, and reduced GI distress is reported in comparison to traditional oral ionic iron. - they reference (Hallberg, Hultén, and Gramatkovski 1997) but I don’t see any mention of side effects in that study.

2. Info and sources regarding inhibitors and enhancers
HIP seems to follow the Heme pathway of absorption. This means that it’s not affected by most the inhibitors, the only one is calcium. Also ascorbic isn’t an enhancer for heme (and therefore most likely HIP)
Heme iron without meat isn’t as effective as heme with meat so animal tissue is likely an enhancer of HIP too.

3. General information
• Heme iron is found in both animal and many plants sources like soy.
• The supplements tend to be sourced form of iron derived from bovine hemoglobin
• Heme Iron contained in a ring structure
• Heme iron is classified as a medical food rather than a supplement, because it is derived from a food (animal) source.

(Tae-Sik Nam 2006)
"Heme-iron products are generally produced by the digestion of Hb with proteolytic enzymes. Depending on the digestion conditions, enzymes used, and drying method, the properties of heme-iron can be altered"
4. References used in this section


