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No advantage of using ferrous bisglycinate as an iron fortificant

Dear Sir:

In the June 2000 issue of the Journal, Bovell-Benjamin et al (1) compared the absorption of iron from ferrous sulfate, ferrous bisglycinate, and ferric triglycinate added to a whole-maize meal. They concluded that iron absorption was better from ferrous bisglycinate than from ferrous sulfate or ferric triglycinate and that ferrous bisglycinate was an effective and safe source of iron that was particularly useful as an iron fortificant in diets rich in phytate. Their other main conclusion was that iron from ferrous bisglycinate does not exchange in the intestinal nonheme-iron pool with the iron from maize or ferrous sulfate.

In comparisons of iron absorption from meals, the percentage absorption, based on tracer methodology, needs to be multiplied by the amounts of iron present in the corresponding labeled pools. Bovell-Benjamin et al concluded that iron from ferrous bisglycinate does not exchange with the iron from maize or ferrous sulfate. This conclusion was based on observations that, when the same amounts of iron as ferrous sulfate and ferrous bisglycinate were given separately together with the maize meal, iron absorption was 1.7% and 6.0%, respectively; when the same amounts of iron were added to the same maize meal, absorption of the tracers was 1.0% and 6.8%, respectively. The authors combined the mean percentage absorption in their studies 1A and 1B, which were then 1.3% and 6.4%, respectively, indicating a 4.7 times greater absorption of iron from ferrous bisglycinate ($P < 0.05$). It is not clear how the conclusion of “no exchange” was drawn between the labels in the intestinal pool in study 1B. However, because the absorption studies were done in the same subjects, the data can be analyzed in a way that is more sensitive and specific by comparing the absorption in the same subjects and not in 2 groups of subjects. The mean absorption of iron from the tracer for ferrous sulfate given alone with maize was 1.7% (study 1A); when ferrous sulfate was given together with maize and ferrous bisglycinate (study 1B) the absorption was lower (1.0%). These mean values suggest that the absorption was different in the 2 studies. When we compared more correctly the individual ratios in absorption of the ferrous sulfate tracer in studies 1A and 1B, this mean ratio was 1.653 ($t = 2.436, P = 0.0375$). A corresponding comparison of ferrous bisglycinate in studies 1A and 1B showed that the absorption was the same when ferrous sulfate was given alone in study 1A and when given together with the same amount of ferrous sulfate in the same meals in study 1B (mean ratio: 0.956, $t = −0.299, P = 0.77$). This implies 1) that the absorption of iron from the nonheme-iron pool dropped by ≈40% (1/1.65) when ferrous sulfate was given together with ferrous bisglycinate and 2) that the percentage absorption of iron from a hypothetical chelate pool of ferrous bisglycinate was not influenced. The most obvious explanation is that some iron moved from “the ferrous bisglycinate pool” to the “maize pool,” which we know from several previous studies is uniformly labeled by the added ferrous sulfate.

All this implies that the iron absorption from ferrous sulfate given with maize in study 1A was measured correctly. However, the absorption of iron from ferrous bisglycinate in study 1A cannot be calculated because we do not know 1) how much iron moved from ferrous bisglycinate to the nonheme-iron pool in maize, and thus 2) how much iron remained in chelate form. We know from study 2A that iron in ferrous bisglycinate is less well absorbed than is ferrous sulfate when given alone. It may be assumed that ferrous bisglycinate is partly dissociated and that an unknown, but possibly considerable, amount of iron is released into the nonheme-iron pool (maize-meal pool). An absolute condition in these kinds of tracer studies is to know the specific activity of the iron.

This would imply that it is impossible to estimate the total amounts of iron absorbed. Actually, the only way to correctly analyze the isotopic exchange between an iron compound and iron in a food is by comparing iron absorption from a biosynthetically radioiron-labeled food (eg, maize) and the iron compound to be tested. An incomplete isotopic exchange between iron in another iron chelate, FeNaEDTA, and biosynthetically radioiron-labeled maize was observed by several investigators (3–5). In unpublished studies in our laboratory we found an absorption ratio of 0.58 ± 0.044 between biosynthetically radioiron-labeled maize and the iron in FeNaEDTA (n = 10). All these results suggest that a fraction of iron chelates may form a separate pool, that some iron is dissociated and exchanges with the nonheme-iron pool, and that some unknown fraction is absorbed from a kind of possible mucosal-iron pool.

An interesting part of the discussion in the present study (1) addressed the process of absorption of iron from the intestines when strong iron chelates are also present. Our assumption is that there is a pool at the intestinal mucosal surface from which iron is taken up by special nonheme-iron receptors. This mucosal pool is directly connected with the nonheme, intraluminal nonheme-iron pool. In that pool, ferric iron is probably reduced to ferrous iron to be absorbable. Iron chelates such as ferrous bisg-
lycinate and FeNaEDTA are present initially in an iron chelate pool that is connected both with the common nonheme intraluminal pool (where an isotopic exchange may take place) and directly with the mucosal nonheme-iron pool, where its iron may be released and absorbed. In this way, iron status influences the absorption from both the iron in the chelate pool (as reported here) and the iron in the usual intraluminal nonheme-iron pool. Such a hypothesis might explain many of the seemingly contradictory results.

On the basis of our analysis of the data presented, we cannot accept the main conclusions drawn by Bovell-Benjamin et al. There is no evidence to support the conclusion that ferrous bisglycinate is useful as an iron fortificant.

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REFERENCES

Reply to L Hallberg and L Hulthén

Dear Sir:

Hallberg and Hulthén question the interpretation of our data that showed that ferrous bisglycinate is absorbed better from whole maize than is ferrous sulfate. Specifically, they question our conclusion that there was no exchange in the intestinal pool between iron from ferrous bisglycinate and iron from ferrous sulfate.

The basis of our conclusion is that absorption of iron from ferrous sulfate and ferrous bisglycinate was the same whether the labeled forms of these compounds were given separately or mixed together in the same meal. Our data were analyzed correctly because it is appropriate to control for the repeated-measures nature of the design. Also, because a log transformation was used, in effect the absorption ratios were compared, not the absolute values. As stated in our article, the average absorption of iron from ferrous sulfate was about one-fifth that of its absorption from ferrous bisglycinate ($P < 0.0001$).

What we did not do was use the repeated-measures procedure to examine the interaction between study and iron source. We have since used that procedure and found the interaction to be significant ($P = 0.01$). It is therefore appropriate to make a comparison of iron sources between studies. This comparison showed that iron absorption from the bisglycinate was the same in each trial ($P = 0.77$, Tukey’s test) but, as noted by Hallberg and Hulthén, the absorption from ferrous sulfate differed between studies 1A and 1B ($P = 0.04$). However, the results do not support their interpretation that there is an exchange between iron from ferrous bisglycinate and the nonheme-iron pool.

If the iron from these sources had exchanged in the intestinal pool there would have been a similar trend in iron absorption from both iron sources in studies 1A and 1B. In fact, the opposite occurred. As the geometric mean absorption ratio of iron from ferrous sulfate between studies 1A and 1B dropped to 0.59, a significant difference, it increased to 1.13 for ferrous bisglycinate, which was not significant. If, as Hallberg and Hulthén suggest, the explanation is that some iron moved from the ferrous bisglycinate into the “maize pool,” which is equilibrated with the ferrous sulfate iron, less label from bisglycinate would have been absorbed in study 1B, and there would have been less of a difference between the geometric absorption means. However, the means became more separated: the ratio of absorption of iron from ferrous bisglycinate to absorption of iron from ferrous sulfate in study 1A was 3.5 and increased to 6.8 in study 1B. In addition, even if the cause of the 41% lower absorption of iron from ferrous sulfate in study 1B was dilution with iron from ferrous bisglycinate, it still could not explain this amount of divergence. Importantly, care was taken to provide the same amount of iron as sulfate or bisglycinate, or both, so that the size of the intestinal iron pool was similar in the 2 studies.

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