

Iron bis-glycine chelate competes for the nonheme-iron absorption pathway

Dear Sir:

Pizarro et al (1) reported that iron bis-glycine chelate (Fe-bis-gly) ionizes in stomach acid to free iron cations, which are absorbed from the intestinal lumen via the nonheme-iron pathway. They stated that these findings contradict those of previously published articles (2–4). If Fe-bis-gly were to hydrolyze before the absorption of its iron component, the released iron cations would compete with iron absorbed from FeSO₄, and the rates of absorption would depend on the relative amounts of free iron dissociated from each source by acid digestion. Several research studies have shown that iron from Fe-bis-gly is preferentially absorbed over iron from FeSO₄ (5–8). The results of studies that used radiolabeled iron indicate that Fe-bis-gly is absorbed intact (4).

Data from the study by Pizarro et al support the intact absorption of Fe-bis-gly by a pathway other than nonheme absorption, on the basis of the following observations: 1) Fe-bis-gly was not directly measured—its effects were surmised on the basis of the absorption of radiolabeled iron from either FeSO₄ or lyophilized hemoglobin both in and out of the presence of unlabeled Fe-bis-gly; 2) ingested Fe-bis-gly does not need to participate in the absorption pathway of FeSO₄ when the 2 compounds are administered together—it is absorbed independently via the mucosal cell receptors that consistently work best for it; 3) there was no significant difference in the absorption of radiolabeled iron from FeSO₄ that had no enteric protection, whether Fe-bis-gly was present or not, which indicated that there was no competition for the nonheme FeSO₄ pathway; 4) absorption of radiolabeled iron from hemoglobin was significantly enhanced (P < 0.01) in the presence of Fe-bis-gly, which indicated an augmenting effect of Fe-bis-gly on the heme uptake pathway; and 5) when FeSO₄ and Fe-bis-gly were administered together with enteric protection, iron absorption from FeSO₄ was significantly suppressed (P < 0.001).

This finding indicates that the iron requirements of the mucosal cells in a high-pH environment were being met by the absorption of iron as Fe-bis-gly, given that there was no other alimentary iron present (because the test subjects had fasted overnight and were prevented from eating for 4 h after dosing).

Bovell-Benjamin et al (4) used different radioisotopes to label the iron in each of FeSO₄ and Fe-bis-gly. They compared the absorption of the 2 sources in whole-maize meal porridge consumed by 10 noniron-deficient, nonanemic, fasted men. After initial whole-blood samples were taken, all of the men received porridge containing ⁵⁹FeSO₄ on day 1 and porridge with ⁵⁵Fe-bis-gly on day 2. On day 14, three 10-mL fasting blood samples were drawn from each test subject, and the contents of both radiolabeled iron compounds were measured in the same samples. On day 16, the same men were given porridge containing both labeled iron sources; blood samples were recovered on day 31 for the measurement of ⁵⁹FeSO₄ and ⁵⁵Fe-bis-gly. Results from the combined tests showed that the absorption of iron from ⁵⁵Fe-bis-gly was 4.7 times that of iron from ⁵⁹FeSO₄, even though both ⁵⁹FeSO₄ and ⁵⁵Fe-bis-gly were obviously down-regulated (r = 0.99, P < 0.001) by iron stores in the individual men. The percentage of iron absorbed from each iron source was unaffected by the presence of the other iron source. This finding indicates that there was no cross-exchange of iron between the 2 sources and that Fe-bis-gly was absorbed intact, because FeSO₄ must release iron before its uptake. This study showed that the characteristics of iron absorption from FeSO₄ and from Fe-bis-gly are different, with Fe-bis-gly being favored when doses of phytate are high.

On the basis of the findings of Pizarro et al, Fe-bis-gly has a relation with the heme-absorbing pathway. Heme is also a chelate, the chelating ligand being cyclic porphyrin. Heme iron is far more bioavailable than are inorganic sources of iron. In a diet containing only 6% of the total iron as heme, 30% of the iron absorbed was acquired from heme, to the exclusion of other dietary sources (9). Pizarro et al found that heme absorption increased significantly (P < 0.01) in the presence of Fe-bis-gly. This indicates that the 2 sources were mutually compatible. Clearly, the uptake of one of the iron compounds was influenced by the presence of the other, which was the criterion that Bovell-Benjamin et al (4) used to assess iron absorption from iron sources. On the basis of this criterion and according to the data of Pizarro et al, heme and Fe-bis-gly share similar absorption properties.

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REFERENCES


Reply to O Pineda

Dear Sir:

The results of our study (1) show that an important fraction of iron from iron bis-glycine chelate (Fe-bis-gly) is delivered to the stomach or duodenum and forms part of the nonheme-iron pool. We do not think that the results of our study contradict those of previously published studies (2–4).

Pineda supports the existence of special nonheme-iron receptors, which take up iron from an iron chelate pool at the intestinal mucosal surface (4, 5). Data from our study do not support this hypothesis. Furthermore, there is neither direct scientific evidence that shows the presence of the intact Fe-bis-gly within the enterocyte nor evidence of the existence of a specific receptor. Differences in the absorption of nonheme-iron sources do not necessarily indicate the existence of different absorption pathways. Differences could be explained on the basis of physical and chemical characteristics that determine different iron bioavailabilities.

There is growing evidence that supports the hypothesis, first proposed by Olivares et al. (2), that a significant but not quantified fraction of iron from Fe-bis-gly is dissociated in the gastrointestinal tract, where it can interact with other dietary constituents and enter the common nonheme-iron pool (4, 6, 7). This hypothesis is supported by studies that showed that 1) iron from Fe-bis-gly is affected by inhibitors and enhancers in the diet, as occurs with nonheme iron but not with heme iron, which is absorbed intact (2, 3, 8), and 2) iron from Fe-bis-gly competes for the nonheme-iron absorption pathway but not for the heme-iron absorption pathway (1). The results of our study, discussed by Pineda in his letter, provide strong evidence supporting our hypothesis. Our study was designed to show the competition of a small trace (0.5 mg) of a labeled ionic iron (ferrous sulfate) and heme iron (hemoglobin) with increasing doses of Fe-bis-gly. We labeled ferrous sulfate and hemoglobin, an approach widely used to assess competition for intestinal uptake, because both compounds have well-known absorption pathways. Whenever 2 compounds compete for the same absorption pathway, their dose-response curves are alike. Pineda argued that the results of the study performed by Bovell-Benjamin et al. (4) support the lack of competition between Fe-bis-gly and nonheme iron. However, we believe that the design of this study did not allow for the characterization of competition because only one low dose of iron (1 mg) with a ratio of Fe-bis-gly to ferrous sulfate of 1:1 was administered. Competition between the 2 compounds cannot be observed under this condition because, despite the greater bioavailability of iron from Fe-bis-gly, the quantity of available iron at this dose and ratio would not be sufficient to saturate the receptors and transporters of iron in the enterocyte. In contrast, this ratio ranged from 1:10 to 1:200 in our study.

Our results showed that Fe-bis-gly did not compete with hemooglobin for the heme-iron absorption pathway. The mild decrease in the dose-response curve for competition between Fe-bis-gly and hemoglobin may have been due to the competition between a small fraction of nonheme iron dissociated from labeled hemooglobin and nonheme iron from Fe-bis-gly.

Differences in the magnitude observed between the dose-response curves of coated ferrous sulfate and Fe-bis-gly can be explained—as Pineda does in his letter—by differences in the bioavailability of both compounds under the environmental conditions of the duodenum. Both curves have a similar trend, with differences only in the magnitude of the changes in absorption of the tracer. If Fe-bis-gly did not compete with the tracer of ferrous sulfate, the trend of the curve would be different.

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REFERENCES

Serum 25-hydroxyvitamin D response to oral vitamin D intake in children

Dear Sir:

In a recent issue of the Journal, Heaney et al. (1) reported important new data on the requirement of oral vitamin D to maintain physiologic concentrations of circulating 25-hydroxyvitamin D [25(OH)D] in adults. Some years ago, an analysis was performed of serum concentrations of 25-hydroxyvitamin D2 [25(OH)D2] and 25-hydroxyvitamin D3 [25(OH)D3] in German pediatric patients (x age: 5.2 y; x body wt: 21.7 kg) with phenylketonuria (n = 3) or maple syrup urine disease (n = 3) during the winter (January–March) and summer (July–September) (2). All patients were free of diseases affecting vitamin D metabolism. They were supplemented daily with doses of 15.6–25.0 μg vitamin D2/d (mean: 19.6 μg vitamin D2/d) for a minimum of 1.5 y, which corresponded to a mean vitamin D2 intake of 1.37 μg · kg body wt–1 · d–1 in winter and of...