

# Advantages and Limitations of Iron Amino Acid Chelates as Iron Fortificants

Lindsay H. Allen, Ph.D.

## Introduction

This review provides information concerning the value of iron amino acid chelates as iron fortificants. Approximately three years ago, the International Life Sciences Institute held a technical consultation on iron amino acid chelates. At that time the available research data was inadequate to form a conclusion concerning the bioavailability of iron from iron amino acid chelates; since then, however, several well designed experiments have investigated the value of these compounds for the fortification of foods. These are described in the present review.

## Structure of Ferrous Bisglycinate and Ferric Trisglycinate

Ferrous bisglycinate (sold commercially as Ferrochel by Albion Laboratories, Clearfield, UT) consists of a molecule of ferrous iron attached to two molecules of glycine. The iron is bound to the carboxyl group of glycine in an anionic bond, and to the amino group in a coordinated, covalent bond, to form two heterocyclic rings. This structure may protect iron from interactions with dietary inhibitors of iron absorption, potentially making it an ideal fortificant for foods high in inhibitors such as phytate. Theoretically, it could also cause less peroxidation of polyunsaturated fatty acids and vitamins than soluble iron. If Ferrochel is absorbed intact, however, it is important to know whether iron absorption from this molecule is normally down-regulated as iron stores increase.

Ferric trisglycinate is also sold commercially as Ferrochel Taste-Free, which is composed of three glycine molecules combined with a ferric iron molecule (Albion Laboratories, Clearfield, UT). The absorption of the ferric iron from the trisglycinate is discussed here briefly, although the majority of this review will be devoted to discussion of the qualities of the ferrous bisglycinate—Ferrochel—as an iron fortificant.

## Recent Studies on the Absorption of Iron from Amino Acid Chelates

The four recent studies reviewed here were conducted by Olivares et al. in Chile,<sup>1</sup> Fox et al. in England,<sup>2</sup> Bovell-Benjamin et al. in the United States,<sup>3</sup> and Layrisse et al. in Venezuela.<sup>4</sup> In all of these studies iron absorption was evaluated by labeling the iron amino acid chelate with radioactive or stable iron isotopes and measuring the amount incorporated into red blood cells approximately two weeks later.

In the research by Olivares et al.<sup>1</sup> the absorption of iron from ferrous bisglycinate in water given to 14 adult women was compared with its absorption from milk in a different group of 14 similar individuals. Only two subjects were iron deficient. Because different subjects were used in each study, and the amount of iron absorbed by each individual is affected by their iron status, all subjects also consumed a reference dose of ferrous ascorbate to correct for interindividual differences in iron status. Ferrochel iron was less well absorbed from the milk (11%) than from the water (46%). Also, adding ascorbic acid increased the absorption of Ferrochel iron from milk by 38%, to 15%. These results suggest that inhibitors and enhancers can affect the absorption of the bisglycinate iron. The authors commented that there was a much larger (approximately 250%) increase in iron absorption, however, when ascorbic acid was added to ferrous sulfate in a previous experiment. Another limitation of this study was that there was no assessment of the absorption of ferrous sulfate iron from milk; the authors reported that in a previous study they found this to be only 4%, which would mean approximately three times more ferrous bisglycinate iron than ferrous sulfate iron is absorbed from milk.

In the study by Fox et al. in England,<sup>2</sup> infants were administered meals containing bisglycinate iron or ferrous sulfate iron labeled with stable isotopes. There was no significant difference in the efficiency of iron absorption from the two iron sources either from a pureed vegetable weaning food or a high-phytate whole-grain cereal weaning food; the phytate reduced the absorption of iron to a similar extent from both fortificants. Impro-

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Dr. Allen is with the Program in International Nutrition, Department of Nutrition, University of California, Davis, CA 95616, USA.

tantly, 0.83 mg ascorbic acid per mg iron was added to the ferrous sulfate, however, which may have caused higher iron absorption in the ferrous sulfate control group than if the ferrous sulfate had been added alone.

In the study by Bovell-Benjamin et al.<sup>3</sup> in the United States, the absorption of iron from ferrous bisglycinate was compared with its absorption from ferrous sulfate. Both sources were fed to the same ten iron-deficient men in a whole-maize porridge with high phytate content. The purpose was to determine if the absorption of Ferrochel iron is protected from inhibition by phytate and whether Ferrochel iron exchanges with ferrous sulfate iron in the intestinal pool. In the first experiment the two sources of iron were fed separately on two consecutive days, and in the second the iron sources were fed together in the same meal. Each iron source was labeled with a different isotope. Had the Ferrochel degraded in the intestine and its iron exchanged with the ferrous sulfate iron, the observed absorption of iron from the two sources would have been identical owing to mixing of the free iron isotopes in the intestinal lumen. When the two iron sources were fed in two separate maize meals, however, iron absorption from the bisglycinate was five to six times higher than from the ferrous sulfate (on average, approximately 6–7% compared with 1–2%, respectively). This discrepancy persisted when the iron sources were mixed together in the same meal, indicating that there was no exchange of the isotopes from the two iron sources in the intestinal pool, and that the ferrous bisglycinate molecule was probably absorbed in an intact form.

In a second study, the same investigators<sup>3</sup> assessed whether the absorption of the iron from Ferrochel is down-regulated normally by higher iron stores. Iron absorption from ferrous ascorbate in water and Ferrochel in water was compared in 21 healthy adult women with a range of iron status (serum ferritin from 2 to 63  $\mu\text{g/L}$ ). When given in water, iron absorption from the bisglycinate was 31% compared with 72% from the ascorbate. Absorption of iron from both compounds was inversely and similarly correlated with iron status ( $r = -0.61$  between ferrous ascorbate and serum ferritin, and  $r = -0.78$  between ferrous bisglycinate and serum ferritin). Finally, the absorption of ferric trisglycinate iron in water (39%) was similar to that of the ferrous bisglycinate iron, but the trisglycinate iron was quite poorly absorbed (2.3%) from the maize porridge meal. In summary, these two studies show the superior absorption of iron from the ferrous bisglycinate in the presence of high phytate and suggest that the bisglycinate iron is taken into the intestinal cells in the chelated form. It is probable, however, that the chelate is degraded within the intestinal cell because the absorption of its iron is regulated normally by iron status.

Layrisse et al. studied iron bioavailability from breakfasts enriched with ferrous bisglycinate to which phytates and polyphenols (iron absorption inhibitors) were added.<sup>4</sup> Five different experiments were conducted in a total of 74 subjects. When ferrous bisglycinate and ferrous sulfate were given together or in different meals (in breads made from corn flour or white wheat flour, with cheese and margarine) the iron absorption from the bisglycinate was twice that from the sulfate although it was slightly less than iron absorption from iron EDTA. The efficiency of iron absorption from the fortified corn flour was 5.1% from ferrous sulfate and 10.1% (significantly higher) from the ferrous bisglycinate; these data support the study by Bovell-Benjamin et al.<sup>3</sup> that found higher absorption of the bisglycinate iron from maize. However, the addition of phytase to the bisglycinate-fortified corn bread did increase iron absorption by approximately 30%, indicating that there was some inhibition of absorption of the bisglycinate iron by phytate. The polyphenols in espresso coffee and tea reduced iron absorption from the ferrous bisglycinate by 50% but there was no ferrous sulfate control for comparison. The investigators concluded that ferrous bisglycinate is a suitable compound for food fortification.

### **Stability of Foods Fortified with Iron Amino Acid Chelates**

In addition to assessing iron bioavailability from the iron amino acid chelates, it is important to evaluate how these iron sources affect the quality of foods to which they are added. The promotion of oxidative rancidity in fats, and associated off-flavors and colors, is a universal problem with most soluble iron fortificants such as ferrous sulfate. Bovell-Benjamin et al.<sup>5</sup> evaluated the effect of the chelates on the quality of whole-maize meal, in which 60% of the total fatty acids are polyunsaturated and therefore particularly susceptible to lipid oxidation. Several fortificants were compared: ferrous sulfate, ferrous bisglycinate, ferric trisglycinate, sodium iron EDTA, and a zero-iron control. Each fortificant was added at 30 or 60 mg iron per kg dry maize meal, and stored at 30, 40, or 50 degrees Celsius for 20 days. The production of hexanal, a breakdown product of lipid peroxidation, was assessed. The ferrous bisglycinate caused more lipid peroxidation than any of the other iron compounds tested. This peroxidation was completely prevented by the addition of the antioxidant butylated hydroxyanisole (BHA) at 25 ppm (lower concentrations were not tested). By contrast, citric acid, tocopherol, and histidine had no protective effect. Ferric trisglycinate did not produce rancidity, presumably because of its lower solubility.

Sensory evaluation by 15 trained evaluators was also conducted to evaluate 16 appearance, flavor, and texture attributes in the same maize samples (treatment de-

scribed in previous paragraph). In general, the color of the maize was not different with either of the two iron amino acid chelates compared with the zero-iron control. The ferrous bisglycinate-fortified samples (but not ferric trisglycinate), however, were significantly more rancid, especially at the higher concentrations and higher storage temperature. Rancidity paralleled the hexanal production values.

Because these trials employed a sensory evaluation panel trained to detect small differences in sensory properties, an additional study was conducted to determine whether untrained individuals, namely young children and their mothers, could detect these differences in the quality of the maize meal stored under the same conditions.<sup>6</sup> In this consumer-acceptance trial, parents were asked to evaluate their own liking of the maize porridge, as well as the reaction of their child to the porridge, on a 9-point hedonic scale. The porridges made from the ferrous bisglycinate-fortified maize were generally as acceptable to young children and their parents as a zero-iron control, and the addition of BHA to the ferrous bisglycinate did not affect the acceptability rating.

Relatively little attention has been paid to the effect of iron on the stability of vitamin mixes to which it is added. Marchetti et al.<sup>7</sup> assessed the effect of adding sulfates versus amino acid chelates of copper, zinc, iron, manganese, and cobalt to mixtures of vitamins stored at either 20 or 37 degrees Celsius for 90 and 180 days. The authors did not describe the exact nature of the chelates (e.g., ferrous bisglycinate or ferric trisglycinate). At 37 degrees Celsius the metal sulfates caused significant losses of vitamins B<sub>2</sub> and B<sub>6</sub>, and at 20 degrees Celsius, losses of ascorbic acid, retinol, and vitamin K. There was significantly less loss when the amino acid chelates were added. After 180 days at 37 degrees Celsius, for example, loss of retinol was approximately 65% with the metal sulfates compared with 46% with the amino acid chelates. Additional studies are needed to document the extent to which specific metal amino acid chelates conserve vitamins in mixes used to fortify foods or to be consumed as supplements. Both the efficacy of the supplements and the cost of the vitamin losses are important considerations.

### Mineral-Mineral Interactions

It is plausible that iron amino acid chelates, if they indeed remain chelated in the intestinal lumen and are taken into the intestinal cells intact, cause less inhibition of the absorption of other minerals such as zinc (especially if the latter is also provided as an amino acid chelate). This issue remains to be investigated.

### Commercial Products Fortified with Iron Amino Acid Chelates

Many commercial products are already fortified with iron amino acid chelates. Amino acid chelates were originally developed for the animal feed industry, which has purchased chelated minerals for many years because of the conviction that their greater efficacy is worth the investment. Ferrous bisglycinate appears to be an excellent fortificant for increasing the iron content of milk; it is used to fortify milk and dairy products sold in Brazil, Chile, Argentina, South Africa, and Italy. Unlike ferrous sulfate, bisglycinate does not change the color or taste of milk, and does not cause peroxidation of the milk lipids even during long-term storage. Reportedly, the bisglycinate needs to be added after the milk is homogenized; the explanation for this may be that a protein layer surrounds the micelles in homogenized milk preventing oxidation of the lipids in the core of the micelle. (Prior homogenization does not prevent the adverse sensory changes caused by ferrous sulfate, however.) Granola, biscuits, cereal products, cookies for children, and fruit drinks are successfully fortified with ferrous bisglycinate providing substantial amounts of iron.

### Cost Considerations

A frequently voiced objection to the use of amino acid chelates is their higher cost relative to ferrous sulfate or other cheaper iron sources. The current cost estimate provided by the manufacturers is approximately \$600/kg or, because it contains 20% iron, \$120/kg iron. If as indicated by the experiments of Bovell-Benjamin et al.<sup>3</sup> and Layrisse et al.<sup>4</sup> described above, the bioavailability of ferrous bisglycinate iron is two to six times higher than that of ferrous sulfate iron, however, it should be possible to add substantially less of the ferrous bisglycinate and achieve the same level of iron absorption. Dr. Dary discusses the relative costs of iron fortificants further in this volume.

### Conclusions

The advantage of using ferrous bisglycinate as an iron fortificant is its much higher absorption from foods that are high in iron absorption inhibitors, such as whole maize. If given in water, or possibly in foods low in inhibitors, the bisglycinate may not provide such a large advantage. Although there is some evidence that ferrous bisglycinate is intact when taken up by the intestinal cells, the efficiency of iron absorption from this source is apparently normally down-regulated by iron status. An additional advantage of the bisglycinate is that it can be used as an iron fortificant for dairy products and is added to a wide variety of commercial products. There may be fewer adverse interactions between ferrous bisglycinate

iron and other vitamins in multivitamin preparations although further studies of this important question are needed. It is also possible, but not known, that amino acid chelates of iron cause less inhibition of the absorption of other minerals such as zinc. A disadvantage of the bisglycinate is its higher redox potential and subsequently greater tendency to cause lipid oxidation in some situations, such as in whole-meal maize. Whereas a trained sensory evaluation panel could detect the adverse effect of ferrous bisglycinate on the sensory qualities of maize meal, however, mothers and young children could not. Moreover, the addition of a small amount of an antioxidant, such as BHA, prevented these sensory changes and the chelate is used to fortify many commercial cereal-based foods. The bisglycinate is a more expensive source of iron than ferrous sulfate, but smaller amounts could be used as a result of its higher bioavailability.

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