Bioavailability of Iron, Zinc, and Copper as Influenced by Host and Dietary Factors

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INTRODUCTION

To determine the mineral intake that will support or enhance performance of military personnel, the bioavailability of the minerals must be considered, in addition to the quantity of the mineral required for biological function. Bioavailability describes the biological utilization of a mineral as consumed, and is affected both by dietary and host factors. This paper briefly summarizes information on the bioavailability of iron, zinc, and copper, emphasizing topics of particular application to setting nutritional guidelines for feeding the military.

IRON BIOAVAILABILITY

Body iron is mainly controlled at the point of intestinal absorption rather than excretion (McCance and Widdowson, 1937), and iron bioavailability is
largely determined by the factors that affect intestinal absorption. Absorbed iron must replace approximately 1 mg of obligatory iron losses daily in men and postmenopausal women, and up to an additional 2.5 mg daily in menstruating women (Institute of Medicine, 2001). Iron absorption is substantially influenced by both host and dietary factors.

Dietary factors that influence absorption include the form of dietary iron (either heme or nonheme), as well as dietary constituents consumed concurrently that help keep nonheme iron reduced and soluble.

Heme iron, the protoporphyrin iron complex that enters intestinal mucosal cells intact, is absorbed more efficiently than nonheme iron. Heme iron accounts for ~40 percent of the iron in meat, poultry, and fish flesh, and constitutes 0–2.5 mg of the dietary iron consumed daily. Absorption of heme iron is enhanced by unidentified factors in meat, poultry, or fish (Layrisse et al., 1968; Martinez-Torres and Layrisse, 1971) and inhibited by calcium (Hallberg et al., 1991) when consumed in the same meal (Box B-1).

Nonheme iron describes the remaining iron in foods, which has been found to form a chemically exchangeable iron pool in the intestinal lumen (Cook et al., 1972). Absorption of this nonheme iron is affected by other dietary constituents consumed in the same meal (Box B-1), that influence the solubility and reduced (ferrous) valence state. Meat, poultry, and fish (Layrisse et al., 1968; Martinez-Torres and Layrisse, 1971) and ascorbic acid (Cook and Monsen, 1977; Hallberg et al., 1986) enhance nonheme iron absorption in a dose-dependent manner, and are especially effective in the presence of inhibitors such as phytic acid and

<table>
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<th>BOX B-1</th>
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<td><strong>Food Components that Enhance or Inhibit Iron Absorption, When Consumed Concurrently</strong></td>
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### Heme Iron Absorption

**Enhancers**
- Meat, poultry, fish

**Inhibitors**
- Calcium

### Non-heme Iron Absorption

**Enhancers**
- Meat, poultry, fish
- Ascorbic acid
- Alcohol
- Retinol?
- Carotene?
- Other organic acids?

**Inhibitors**
- Phytic acid
- Polyphenols/tannins (tea and coffee)
- Soy protein
- Egg
- Calcium
- Antacids

**Interactions**
- Ascorbic acid or meat, poultry, and fish—enhancing effects are greater with phytate or polyphenols

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polyphenols (Hallberg et al., 1989; Hallberg and Hulthen, 2000). Alcohol enhances nonheme iron absorption, possibly by enhancing gastric acid secretion which promotes the reduced valence state (Hallberg and Hulthen, 2000). Carotenes been reported as enhancers of nonheme iron absorption (Garcia-Casal et al., 1998; Layrisse et al., 2000). Reports of enhancement by retinoids are inconsistent (Garcia-Casal et al., 1998; Layrisse et al., 2000; Walczyk et al., 2003). Citric, malic, and tartaric acids enhance nonheme iron absorption at a high (100-fold) molar ratio (Gillooly et al., 1983), which may not be practically relevant.

Inhibitors of nonheme iron absorption include phytic acid (inositol hexaphosphate, the main food form of inositol phosphates) in whole grains, legumes, lentils, and nuts (Gillooly et al., 1983; Hallberg et al., 1989); iron-binding polyphenols, such as flavonoids, phenolic acids, and their polymerization products, in tea, coffee, red wines, and a variety of other cereals, vegetables, and spices (Brune et al., 1989; Gillooly et al., 1983; Hallberg and Hulthen, 2000); soy protein (apparently independent of the phytic acid in soy), (Hurrell et al., 1992); and eggs (Callender et al., 1970; Hallberg and Hulthen, 2000; Hurrell, 2003). Calcium inhibits the absorption of both nonheme as well as heme iron (Cook et al., 1991; Hallberg et al., 1991). Zinc in a 1:5 iron:zinc molar ratio reduces iron absorption when given with water, but not with a meal (Rossander-Hulten et al., 1991). Supplemental zinc in equimolar quantities may inhibit iron absorption (Crofton et al., 1989) and impair the iron status of women with low iron reserves (Donangelo et al., 2002). Extensive research on dietary iron bioavailability has helped quantify dose effects and interactions, and algorithms have been developed to calculate the iron bioavailability of diets (Hallberg and Hulthen, 2000; Reddy et al., 2000), but these need further validation.

Host factors that influence iron absorption include iron stores, erythropoiesis, hypoxia, pregnancy, and inflammation (Finch, 1994; Miret et al., 2003). Iron absorption is inversely related to iron status (Cook, 1990; Hallberg et al., 1997; Lynch et al., 1989; Roughhead and Hunt, 2000; Taylor et al., 1988). With serum ferritin concentrations from 300 to ~5 μg/L, heme iron absorption can differ by nearly 3-fold, from approximately 20 to 50 percent, and the efficiency of nonheme iron absorption (from a high bioavailability diet) is influenced to a greater extent, from less than 1 to over 35 percent. Recent high iron intake reduces nonheme (Hoglund, 1969) but not heme iron absorption, independent of detectable changes in serum ferritin (Roughhead and Hunt, 2000). The genetic mutation associated with hemochromatosis in people from Northern Europe results in increased absorption of both heme and nonheme iron (Lynch et al., 1989). About 10 percent of those populations are heterozygous for the same mutation, but this does not appear to increase iron absorption (Hunt and Zeng, 2004; Roe et al., 2005). However, additional genetic as well as environmental factors may influence an increasing occurrence of high serum ferritin with age, especially in adult men (IOM, 2001). Chronic inflammation is associated with anemia (e.g., anemia of chronic disease) which may partly be the result of reduced iron absorption.
Control of these host factors affecting iron absorption appears to involve the polypeptide hepcidin, which is secreted from the liver in response to high iron stores or infectious stimuli, and both down-regulates intestinal iron absorption and stimulated macrophage iron uptake, reducing serum iron (Ganz, 2003). Inflammatory stress from heavy exercise and exertion may initiate a sequence of increased IL(interleukin)-6 production (Margeli et al., 2005), followed by production of hepcidin (Nemeth et al., 2004), and possibly reduced iron absorption, although the latter has not been clearly demonstrated.

Gender does not directly influence iron absorption: men and women with the same iron status absorb iron similarly. However, women of child-bearing ages have considerably lower iron status than men: the 5th, 50th, and 95th percentiles for serum ferritin are 9, 37, and 124 for U.S. women and 42, 118, and 263 for men, respectively (IOM, 2001). In the U.S., iron deficiency in women of childbearing age is more common among minorities (8–10 percent in White, non-Hispanics vs. 15–19 percent in Black, non-Hispanics and 19–22 percent in Mexican Americans) and those with low income (Looker and Cogswell, 2002; Looker et al., 1997). Because of their reduced iron status, menstruating women absorb nondiurnal iron about twice as efficiently as men (Hunt, 2003b). Women with low iron stores can absorb 25–30 percent of the iron from a diet with high bioavailability, or as much as 3–4 mg iron daily. However, absorption by such women can be substantially reduced by factors that decrease dietary iron bioavailability, such as low meat intake, high phytic acid, and tea consumption (Hunt, 2003b).

Iron absorption can vary at least 15-fold relative to body iron stores, and 6-to-10-fold relative to dietary bioavailability, from diets with similar total iron content. However, these substantial differences in iron absorption, as measured with isotopic tracers, are slow to influence clinical indices of body iron status. In controlled trials of weeks or months duration, serum ferritin was unresponsive to differences in ascorbic acid (Cook et al., 1984; Garcia et al., 2003; Hunt et al., 1994; Malone et al., 1986; Monsen et al., 1991) calcium (Minihan and Fairweather-Tait, 1998; Sokoll and Dawson-Hughes, 1992), or several dietary factors affecting iron absorption by 4-to-6-fold (Hunt, 2003b; Hunt and Roughhead, 2000; Hunt and Roughhead, 1999). Dietary changes apparently require months or years to influence body iron stores, but such differences have been observed with cross-sectional studies of vegetarians, who consistently have lower iron stores than omnivores (Hunt, 2003a). Likewise, serum ferritin was positively associated with ingestion of heme iron, supplemental iron, dietary vitamin C, and alcohol and negatively associated with coffee drinking, in a cross-sectional study of elderly subjects (Fleming et al., 1998).

Changes in iron status are also relatively gradual with iron supplementation: serum ferritin increased by 4–5 μg/L with 20 mg iron as FeSO₄ daily for 6 weeks (Hinton et al., 2000), and 10–12 μg/L with 50 mg iron as FeSO₄ daily (with meals) for 12 weeks (Roughhead and Hunt, 2000). Women with low iron stores
were unable to maintain the difference in serum ferritin achieved with 12 weeks supplementation for 12 weeks after supplements were discontinued (Roughead and Hunt, 2000). These data suggest that to improve the iron status of women with low iron stores (serum ferritin < 20 μg/L) within several weeks, supplemental doses of 20–50 mg nonheme iron/day may be required on a continuing basis. Somewhat more positive results occurred with supplements containing 11 percent of the iron in the heme form: 9 or 27 mg daily iron increased serum ferritin by ~5 (a nonsignificant difference) or 12 μg/L (p < 0.05), respectively, and increased hemoglobin values from ~136 to 142 g/L (p < 0.05) in women with low iron stores (Fogelholm et al., 1994). These changes occurred within 1 month, with little change in 5 more months of supplementation (Fogelholm et al., 1994).

A ranking of the bioavailability to humans of iron salts used for fortification is likely determined by iron valence and solubility (ferrous sulfate, ferrous succinate, ferrous lactate, ferrous fumarate, ferrous glycine sulfate, ferrous glutamate, ferrous gluconate, > ferrous citrate, ferrous tartrate, ferrous pyrophosphate > ferric sulphate, ferric citrate) (Brise and Hallberg, 1962). Chelated forms of iron such as sodium iron ethylenediaminetetraacetic acid (NaFeEDTA) or ferrous bis-glycinate are highly bioavailable and in comparison to iron salts, are less influenced by inhibitors such as phytic acid (Bovell-Benjamin et al., 2000; Hurrell, 2002). Iron fortification sources such as ferric pyrophosphate, ferric orthophosphate and elemental iron powders are relatively inert in dry foods, minimizing adverse chemical reactions that may impair food color, taste, and shelf-life, but also reducing iron absorption relative to salts such as ferrous sulfate. Some micronization and emulsification technologies appear to improve the bioavailability of ferric pyrophosphate (Fidler et al., 2004) and may be useful with other iron forms. The bioavailability of elemental iron powders, composed of relatively pure iron metal with a zero valence state, is inversely related to particle size, surface area, and solubility, and differs according to specific production processes; the bioavailability to replete anemic rats is greatest for carbonyl, followed by electrolytic, and then the several reduced iron powders (Swain et al., 2003). However, the bioavailability of elemental iron powders is difficult to determine sensitively in humans because the commercial powders cannot be isotopically labeled.

**ZINC BIOAVAILABILITY**

Both zinc absorption and excretion adaptively adjust to control body zinc in animals with zinc intakes from marginal to luxuriant (Hunt et al., 1987; Weigand and Kirchessler, 1976a; Weigand and Kirchessler, 1976b). Humans absorb zinc more efficiently when dietary zinc is low (Lee et al., 1993; Taylor et al., 1991; Wada et al., 1985), but this at least partly reflects the immediate effect of the amount ingested, rather than a long-term adaptation to changed zinc intake (Sandström and Cederblad, 1980; Sandström et al., 1980). As more zinc is in-
gested, absorptive efficiency decreases considerably, but the absolute amount absorbed increases.

Several dietary factors may influence human zinc absorption (Lonnerdal, 2000). The zinc content and phytate content, or phytate-to-zinc molar ratio are primary factors, and these are applied in a dietary algorithm for estimating fraction zinc absorption from adult diets (International Zinc Nutrition Consultative Group [IZiNG], 2004). Most of the zinc in Western diets is derived from animal foods, with beef supplying about a quarter of dietary zinc (Subar et al., 1998), which is highly bioavailable. Plant sources such as legumes, whole grains, nuts and seeds are also rich in zinc, which is less bioavailable because these sources are also high in phytic acid, a zinc chelator (Harland and Oberleas, 1987). Mixed or refined diets have phytate:zinc molar ratios of 4–18, whereas unrefined cereal based diets can range from 18 to 30 (IZiNGC, 2004). Although phytic acid in unrefined foods reduces fractional zinc absorption, the higher zinc content of these foods may make these foods preferable to more refined products. For example, nearly 50 percent more zinc was absorbed from a serving of whole wheat, compared with white bread (0.22 versus 0.15 mg, respectively), because the zinc content of the whole wheat bread more than compensated for a less efficient absorption of zinc (16.6 compared to 38.2 percent, respectively) (Sandström et al., 1980).

Zinc bioavailability is enhanced by dietary protein when zinc content is constant (Sandström et al., 1980), but this may differ with specific sources of protein (Davidsson et al., 1996), and the practical importance of protein may be confounded by the food zinc content, which correlates directly with protein content. Women tested with diets high or low in meat (replacing refined carbohydrates) absorbed zinc with similar efficiency, so the amount absorbed was proportional to the nearly 2-fold difference in dietary zinc content (Hunt et al., 1995).

Calcium has been proposed to reduce zinc absorption, but tests are equivocal with calcium either reducing (Wood and Zheng, 1997) or not influencing human zinc absorption (Dawson-Hughes et al., 1986; Lonnerdal et al., 1984; Spencer et al., 1984). Calcium is more likely to inhibit zinc absorption in the presence of phytic acid, by forming insoluble complexes (Fordyce et al., 1987). However, this 3-way interaction has not been clearly demonstrated in humans (Lonnerdal, 2000), and was not observed when calcium was added to a soy-based infant formula (Lonnerdal et al., 1984), or when dairy products (sources of protein as well as calcium) were added to whole wheat bread, a source of phytic acid (Sandström et al., 1980).

Other divalent cations could interfere with zinc absorption by competing for transport sites. Iron reduces zinc absorption when administered using supplemental amounts of inorganic salts (iron:zinc molar ratios of 25:1), but zinc absorption is unaffected in the presence of a food matrix or with more moderate ratios of iron and zinc (iron:zinc molar ratios of 2.5:1) (Lonnerdal, 2000;
Sandström et al., 1985; Solomons and Jacob, 1981; Whittaker, 1998). Supplementing diets with 2 mg copper did not affect zinc absorption by young or elderly adults (August et al., 1989).

Because women generally consume less food, including less dietary zinc, the efficiency of zinc absorption from typical diets is likely to be somewhat greater for women than men. For instance, using experimental diets based on representative U.S. diet surveys, women absorbed 29 ± 8 percent, or 2.3 mg zinc from a diet containing 7.8 mg zinc and 1,570 kcal, and men absorbed 22 ± 4 percent, or 3.1 mg zinc from a diet containing 14.0 mg and 2,545 kcal (Hunt et al., 1992).

It is difficult to evaluate the impact of zinc bioavailability on zinc nutrition since there are no sensitive clinical indices of marginal zinc status. Plasma zinc does not correlate with zinc absorption measurements (Hunt et al., 1995) and has been relatively insensitive to several weeks of severe dietary zinc restriction (Johnson et al., 1993; Wada et al., 1985). However, iron supplementation reduced plasma zinc in a study of pregnant Peruvian women (O’Brien et al., 1999). Plasma zinc was also reduced in research volunteers several weeks after changing to a vegetarian diet (Hunt et al., 1998; Srikumar et al., 1992), and was correlated inversely with dietary phytate:zinc molar ratios in adolescent girls consuming lacto-ovo-vegetarian diets (Donovan and Gibson, 1995), but usually has not differed between vegetarians and non-vegetarians in cross-sectional studies (Anderson et al., 1981; Donovan and Gibson, 1995; Kies et al., 1983; Krajacicova-Kudlackova et al., 1995; Latta and Liebman, 1984). Because of lower zinc absorption, people consuming vegetarian diets, especially with phytate:zinc molar ratios exceeding 15, may require 20 to 50 percent more zinc than nonvegetarians (Hunt et al., 1998; IOM, 2001).

Zinc sulfate and zinc oxide are relatively inexpensive and are the forms of zinc most commonly used for food fortification (IZiNCG, 2004). Although zinc sulfate is much more soluble in water than zinc oxide, the two forms have been found equally well absorbed when used to fortify wheat products (de Romana et al., 2003; Herman et al., 2002). In addition to these two forms, zinc chloride, zinc gluconate, and zinc stearate are generally recognized as safe by the U.S. Food and Drug Administration.

**COPPER BIOAVAILABILITY**

Much less information is available about the bioavailability of copper. Good food sources include organ meats, seafood, nuts, seeds, whole grains, and chocolate. Absorptive efficiency is inversely proportional to dietary copper content. For example, young men consuming diets containing 0.8, 1.7, or 7.5 mg/day absorbed 12, 36, and 56 percent of the dietary copper (Turnlund et al., 1989). Similarly, the greater copper content of an experimental vegetarian diet was associated with a lower fractional apparent absorption, but more total copper
absorbed, despite a 3-fold greater phytic acid content compared to a nonvegetarian diet (Hunt and Vanderpool, 2001). Copper absorption was not reduced by supplemental ascorbic acid (Jacob et al., 1987) or by phytic acid or cellulose (Turnlund et al., 1985).

Compared with men, women tended to absorb copper from similar meals slightly more efficiently, which may compensate for a typically lower dietary copper intake (Johnson et al., 1992). Copper absorption was not different between young and elderly adults (Johnson et al., 1992; Turnlund et al., 1988).

High zinc intakes can reduce copper absorption (IOM, 2001), and zinc supplements have been used to treat Wilson’s disease, an inherited disease that results in copper toxicity (Brewer et al., 1983).

CONCLUSIONS

The bioavailability as well as the content of iron, zinc and copper should be considered when planning military diets. The bioavailability of these nutrients is generally high in North American diets, but bioavailability can be reduced by food choices such as the selection of a vegetarian diet. Biochemical indices are available to assess iron, but not zinc or copper nutritional status. Approximately 20 percent of menstruating women have low iron stores, and iron deficiency is more prevalent in minorities and those of low income. To address iron deficiency in these women, food-based approaches, including food fortification, are likely to require months or years to influence iron status, and would unnecessarily increase bioavailable iron for men. Iron supplementation should be evaluated for these specific women, or perhaps for all military women.

REFERENCES


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