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Workshop Report

Iron bioavailability: UK Food Standards Agency workshop report

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The UK Food Standards Agency convened a group of expert scientists to review current research investigating factors affecting iron status and the bioavailability of dietary iron. Results presented at the workshop show menstrual blood loss to be the major determinant of body iron stores in premenopausal women. In the presence of abundant and varied food supplies, the health consequences of lower iron bioavailability are unclear and require further investigation.

Iron bioavailability: Food Standards Agency workshops

The UK Food Standards Agency (FSA) convened a workshop on 10 October 2003 to review and evaluate current knowledge regarding factors that affect the bioavailability of dietary iron (Fe) and Fe status. Results from recently completed studies were presented – both FSA- and non-FSA-funded – and the workshop was chaired by Professor John Beard.

Background

Fe exists in two valency states: ferrous (Fe^{2+}) and ferric (Fe^{3+}) Fe. The ability of Fe to exist in two redox states is central to its functions in the body: as a carrier of oxygen to the tissues from the lungs; as a transport medium for electrons within cells; as an integrated part of various enzyme reactions. The majority of functional Fe present in the body is as Hb; the remainder is present as myoglobin, haem and non-haem enzymes and transferrin-bound Fe. The majority of storage Fe is present in the liver, spleen and bone marrow.

Fe is stored mainly as ferritin, a spherical protein with Fe atoms enclosed within its core. High concentrations of ferritin are found in the liver, spleen and bone marrow and very small amounts are present in the plasma. Fe is transported in the bloodstream bound to the protein transferrin and uptake by cells is mediated by a cell-surface transferrin receptor, which is expressed in proportion to the cell's requirement for Fe.

Dietary Fe exists in two forms: haem Fe, present in foods of animal origin as Hb and myoglobin; non-haem Fe, found in cereals, pulses, beans, vegetables and meat. Other sources of non-haem Fe in the diet are from fortification of various foods such as cereals and flour, from Fe supplements, and from contamination, for example, from cast-iron cookware.

Physiological losses of Fe from the body are very small and Fe homeostasis is maintained by tight regulation of intestinal absorption (Wessling-Resnick, 2000). For adults, physiological Fe requirements are quite constant and determined by body size, body Fe stores and, in menstruating women, the magnitude of menstrual Fe losses. The absorption of Fe from the diet changes considerably in relation to Fe requirements. More Fe is absorbed from the diet in a state of Fe deficiency and less in a state of Fe repletion. A strong inverse correlation has been demonstrated between Fe absorption and the level of body Fe stores (as determined by serum ferritin (sFn) concentrations) (Hallberg *et al.* 1995). Polymorphisms in a number of genes, thought to regulate Fe absorption and transport around the body, also affect absorption, for example, the *HFE* gene (Feder *et al.* 1996) and genes encoding transferrin receptor 2, ferroportin-1 and hepcidin (Camaschella *et al.* 2002; Roetto *et al.* 2003).

Abbreviations: Hb, haemoglobin; FSA, Food Standards Agency; sFn, serum ferritin; TfR, transferrin receptor.

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Assessment of body-tissue iron

Fe deficiency is usually characterised in three well-defined stages, beginning with depleted Fe stores, followed by Fe-deficient erythropoiesis, and culminating in iron-deficiency anaemia (Cook, 1999). There are a number of biochemical indices to assess body-tissue Fe including Hb concentration, sFn concentration, transferrin saturation, serum transferrin receptor concentration (TfR; a soluble fragment of the intact receptor) and total Fe-binding capacity of serum. The different parameters are affected at different levels of Fe depletion and indicate the stage of Fe deficiency.

Body Fe stores are positively associated with sFn concentrations (Finch *et al.* 1986). Low sFn concentrations can identify iron-deficiency anaemia; however, a large variety of disorders elevate the sFn independently of Fe status. Ferritin is an acute-phase protein, which is increased in inflammation and mild infection (Hulthen *et al.* 1998); adjustment for this enhances its utility. It is also possible that sFn concentrations may relate to Fe turnover rather than Fe stores.

The continued depletion of Fe stores reduces the amount available for erythropoietic cells to use in Hb synthesis. This is characterised by a decrease in serum Fe and an increase in total Fe-binding capacity of serum, resulting in a drop in transferrin saturation and an increase in TfR concentration. The plasma Fe transport variables, serum Fe, total Fe-binding capacity and transferrin saturation, are also affected by a wide range of disorders. Elevated serum TfR is an early event in Fe deficiency and has the advantage of being unaffected by inflammation and infection (Ferguson *et al.* 1992); however, the assay has not yet been standardised to enable comparisons between studies.

The final stage of iron-deficiency anaemia is the exhaustion of the body's Fe stores resulting in severe impairment of Hb synthesis and consequential decrease in Hb concentration. Use of this measure to assess Fe status is limited because anaemia can also be caused by a number of other conditions, including vitamin B_{12} and folate deficiency, as well as genetic disorders.

For the assessment of Fe status it is preferable to use a combination of indictors that provide information about the entire range of deficiency, as no single indicator is sufficiently specific or sensitive.

Iron status of the UK population

Dr Ann Prentice presented evidence on Fe intakes and Fe status indices obtained from five nationally representative surveys of different age- and sex-groups in the UK during the past two decades (Gregory *et al.* 1990, 1995, 2000; Finch *et al.* 1998; Henderson *et al.* 2003; Ruston *et al.* 2004). Dietary intakes were estimated by 4 or 7 d weighed intakes and Fe status by Hb, sFn and transferrin saturation. Approximately 1700–2200 participants in each survey provided dietary information, of which a large proportion provided a blood sample for analysis.

Between 5–10 % of those aged under 18 years were found to have a low Hb concentration. Among older children, it was usually the girls who had the poorest Fe status; this was most notable in those with a vegetarian lifestyle, of whom 30 % had a low Hb concentration (Thane *et al.* 2003). No distinction was made, however, between those with a history of vegetarianism, who usually have a healthier diet, and those who had recently adopted a vegetarian lifestyle. High vitamin C intakes were found to be associated with higher Hb levels.

For infants, a higher prevalence of poor Fe status was observed in those with a high intake of cows' milk or those who had been weaned early (Thane *et al.* 2000). There was evidence of poor Fe status across the age range of children, which was more common in those with various indicators of social disadvantage. Among individuals aged over 65 years, 10 % of free-living individuals and 45 % of individuals living in institutions had a low Hb concentration. In the 1986–7 survey of adults, 20 % of women had a low Hb concentration, although the proportion of men with poor Fe status was relatively low. In the 2000–1 survey of adults, 8 % of women and 3 % of men had Hb concentrations indicative of anaemia and 11 % women and 4 % men had sFn levels below the normal range, increasing to 16 % of women in the 19–24 group.

A substantial proportion of dietary Fe intakes were below the lower reference nutrient intake in many age groups, most notably among adolescent and adult women. Fe fortification made a substantial contribution to Fe intakes; for example, 24 % of the intake of 4–18-year-old children. In general, the surveys found little association between indicators of Fe status and dietary Fe intakes.

Iron bioavailability

Erythrocyte incorporation of Fe isotopes provides a direct measure of bioavailability (Fairweather-Tait, 2001). Foods or meals are extrinsically labelled with Fe isotopes (radio or stable) and the percentage of the isotope which has been incorporated into Hb is measured 14 d later. This is based on the assumption that 80–100 % of the absorbed Fe is incorporated into erythrocytes. This technique has been utilised to demonstrate that the bioavailability of dietary Fe is determined by the chemical form, composition of the meal, as well as physiological factors related to the host, particularly Fe status.

Haem Fe is absorbed more efficiently from the diet (20–30 %) (Martinez-Torres & Layrisse, 1971) than non-haem Fe (5–15 %) (Food and Agriculture Organization & World Health Organization, 1988). Haem Fe is highly bioavailable because it is absorbed intact. In contrast, non-haem Fe enters an exchangeable pool and is affected by the many compounds present in the meal. These compounds impact on solubility, oxidation state, and amounts of 'free Fe' and alter the Fe available for uptake by specific transporters on the surface of enterocytes in the upper intestine.

Calcium (Ca) has been shown to inhibit the uptake of both haem and non-haem Fe (Hallberg *et al.* 1991; Cook *et al.* 1991), although one study reported an inhibitory effect on haem Fe only (Roughead *et al.* 2005). Absorption of haem Fe appears unaffected by other dietary components. Absorption of non-haem Fe is enhanced by ascorbic acid from fruits and vegetables (Hallberg *et al.* 1986; Ballot *et al.* 1987) and by the digestion products of muscle tissue (Cook & Monsen, 1976; Lynch *et al.* 1989). The major dietary inhibitors of non-haem Fe absorption are phytic acid in cereals (Gillooly *et al.* 1984; Hallberg *et al.* 1987) and legumes (Lynch *et al.* 1984; Hurrell *et al.* 1992), as well as phenolic

compounds from beverages such as tea (Disler *et al.* 1975), coffee (Hallberg & Rossander, 1982), cocoa (Hurrell *et al.* 1999), red wine (Bezwoda *et al.* 1985) and herb teas (Hurrell *et al.* 1999).

Professor Richard Hurrell presented results from single-meal Fe absorption studies, using the extrinsic-labelled radio-iron technique, which demonstrated that phytate degradation in cereals, using added or native phytases, improves Fe absorption (Hurrell *et al.* 2003). Phytate-free and native phytate porridges (based on rice, wheat, maize, oat, sorghum, and a wheat–soya blend) were reconstituted with water or milk (wheat only) and Fe absorption was measured in adult human subjects. Fe absorption from the cereal porridges prepared with water and containing their native phytate content was relatively low (0·33 % for oat to 1·8 % for maize). Fe absorption from the cereal porridges was increased significantly by the degradation of phytic acid, although the magnitude of the increase differed markedly. Dephytinisation had no influence on Fe absorption of wheat porridge reconstituted with milk. Although dephytinisation increases Fe absorption, 95 % degradation was necessary for it to be effective.

Cooking procedures, such as bread-making, which includes a yeast fermentation step and degrades phytic acid, have also been shown to improve Fe absorption from cereals (Hurrell *et al.* 2002).

A study in Venezuelan subjects suggested the addition of vitamin A to maize bread increased Fe bioavailability (Garcia-Casal *et al.* 1998); however, a subsequent study in Swiss and Swedish subjects found that vitamin A added to maize bread had no influence on Fe bioavailability (Walczyk *et al.* 2003). The higher vitamin A status of the subjects was considered a possible reason why no effect was observed. However, the addition of vitamin A to maize porridge fed to Ivorian children, a population with low vitamin A status and low Fe status, had the effect of decreasing Fe bioavailability (Davidsson *et al.* 2003). This demonstrates the difficulty in extrapolating results from bioavailability studies of healthy subjects in developed countries to subjects with multiple micronutrient deficiencies in developing countries.

As discussed earlier, there is a high prevalence of poor Fe status in premenopausal women in the UK. Professor Sue Fairweather-Tait presented results from an FSA-funded study that examined Fe bioavailability and status in premenopausal women (*n* 90; aged 18–45 years) allocated to one of three dietary groups (*n* 30) according to their usual diet: lacto-ovo-vegetarian; poultry and fish but no red meat; and red meat (Harvey *et al.* 2005). Habitual dietary Fe intakes were assessed using 7 d duplicate diet collection. Direct measures were made of menstrual blood loss. Fe status (Hb, sFn, TfR, transferrin saturation) was determined from fasting blood samples taken on three consecutive mornings. Fe absorption was measured over 2 d (six meals in total) using a faecal-monitoring stable-isotope technique (Minihane & Fairweather-Tait, 1998).

The red meat group had a lower Fe intake than the vegetarians, but there were no differences between the poultry and fish group and the other two dietary groups. The red meat group had lower sFn concentrations than the poultry and fish group, but there was no difference between the vegetarian group and the other two dietary groups. When the Fe assessment measures were considered together, however, there appeared to be no differences between the groups. There were no differences between the three dietary groups in non-haem Fe absorption from the test meals, but Fe absorption from the test meals was inversely correlated with sFn concentrations. There was a strong inverse correlation between menstrual Fe loss and sFn concentrations.

Although dietary group was associated with Fe status, total Fe intake was not and menstrual blood loss was the main determinant of Fe status in premenopausal women. Fe status was the main determinant of Fe absorption.

Professor Catherine Geissler presented results from an FSA-funded study which tested a predictive model of Fe bioavailability from mixed meals, based on measuring Fe absorption using serum Fe curves in groups (*n* 10) of anaemic women (Conway *et al.* 2006). Single-meal studies of non-haem Fe absorption observed the promoting effect of vitamin C and the inhibitory effect of Ca, phytate and polyphenols; these were used to construct a database on which the algorithm was based. The values obtained using the serum Fe method were shown to correlate with the erythrocyte incorporation of Fe isotope technique. Correlations of measured percentage Fe recovery with percentage absorption predicted from several different models provided similar results with approximate values of *r* 0·5. The results from this study are applicable to anaemic females. Although prediction equations to estimate Fe absorption are simplistic, they can provide quantitative information on the relative bioavailability from complex meals.

Discussion

It has been suggested that vegetarians may have suboptimal Fe nutrition, due to the absence of haem Fe and meat in their diets and generally higher quantities of inhibitors of Fe absorption, for example, phytate, tannins and Ca (Hallberg & Hulthén, 2000). Vegetarians have been reported to have lower sFn concentrations than omnivores, despite total dietary Fe intakes being similar (Worthington-Roberts *et al.* 1988; Reddy & Sanders, 1990; Alexander *et al.* 1994; Ball & Bartlett, 1999). A review of studies examining the prevalence of iron-deficiency anaemia in vegetarians, however, found that only three out of eleven studies reported a higher incidence in vegetarians (Hunt, 2002). Results presented at the workshop suggest vegetarian women have similar Fe intakes and status to omnivores.

Although dietary Fe bioavailability influences Fe absorption from single meals by as much as 10-fold (Hallberg & Hulthén, 2000), longitudinal studies lasting weeks or months indicate little or no responsiveness of body Fe stores (estimated from sFn) to changes in dietary Fe bioavailability (Hunt & Roughead, 1999, 2000), including changes in intakes of ascorbic acid (Cook *et al.* 1984; Hunt *et al.* 1994), Ca (Sokoll & Dawson-Hughes, 1992; Minihane & Fairweather-Tait, 1998) and meat (Hunt *et al.* 1995).

Human subjects can adapt to a wide range of Fe requirements and intakes by the regulation of absorption (Cook, 1990). Fe deficiency upregulates mucosal Fe transporters, such as divalent metal ion transporter, which increase the uptake of non-haem Fe (Wessling-Resnick, 2000). Compared with single-meal studies, multiple-meal studies have observed smaller effects of dietary inhibitors and enhancers on Fe absorption, for example, for Ca (Cook *et al.* 1991), vitamin

C (Cook & Reddy, 2001), fibre (Tidehag *et al.* 1996) and meat (Reddy *et al.* 2006).

Absorption of non-haem, but not haem, Fe was shown to decrease over 12 weeks in men and women receiving Fe supplements (Roughead & Hunt, 2000). Non-haem Fe absorption was shown to partially adapt to differences in Fe bioavailability in men; the difference in total Fe absorption between high- and low-bioavailability diets was reduced from 8-fold to 4-fold when initial absorption was compared with the absorption tested after consumption of the diets for 10 weeks (Hunt & Roughead, 2000). A similar study in premenopausal women who tended to have low sFn concentrations (Hunt, 2003) found that less Fe was absorbed over time with a high-bioavailability diet and more Fe was absorbed over time with a low-bioavailability diet; however, the extent of the adaptation was of a low magnitude and less than that observed in men. Total Fe absorption was related to sFn concentrations for the high-, but not the low-, bioavailability diet, and, although haem Fe was absorbed more efficiently than non-haem Fe, the greater total Fe absorption by women with low Fe stores was mainly attributable to non-haem Fe. This emphasises the potential importance of Fe bioavailability in women with low Fe stores.

Results presented at the workshop show menstrual blood loss to be the major determinant of body Fe stores in premenopausal women, while dietary composition appeared largely unrelated to Fe status. A prospective study in the USA of 620 premenopausal women did observe weak correlations between sFn concentrations and haem Fe intake, red meat intake, Fe supplementation and alcohol, and a negative correlation with phytate (Liu *et al.* 2003). In developed countries, sFn concentrations appear to be less responsive to changes in dietary Fe bioavailability than to blood loss, for example, phlebotomy and menstruation, and Fe supplementation (Mei *et al.* 2005).

Recommendations

The following research recommendations were identified:

(1) Prospective studies are required to investigate determinants of Fe status, especially in infants and young women, and to determine the long-term health consequences of low Fe status;
(2) Further research should be directed towards subject effects, for example, genotype, ethnicity, age, on Fe absorption;
(3) Future Fe bioavailability studies should be based on the whole diet rather than single meals and take account of nutrient interactions and adaptation;
(4) Development of data on Fe status of women during pregnancy, infants, and children;
(5) Improvement of food composition databases to enable more accurate assessment of Fe intakes, for example, haem Fe content.

Participants

Professor John Beard, Pennsylvania State University, USA; Dr Ann Prentice, MRC Human Nutrition Research; Professor Lena Rossander-Hulthén, Göteborg University, Sweden; Professor Richard Hurrell, Swiss Federal Institute of Technology, Switzerland; Professor Sue Fairweather-Tait, Institute of Food Research; Professor Catherine Geissler, King's College London; Dr John Lewis, Central Science Laboratory; Professor Peter Aggett, Lancashire Postgraduate School of Medicine and Health; Professor Mark Worwood, University of Wales College of Medicine; Professor Harry McArdle, Rowett Research Institute, Aberdeen; Dr Robert Simpson, King's College London; Dr Paul Sharp, Surrey University; Dr Linda Harvey, Institute of Food Research; Dr Mark Roe, Institute of Food Research; Dr Birgit Teucher, Institute of Food Research; Dr Jack Dainty, Institute of Food Research; Dr Janet Cade, Leeds University; Dr Chris Bates, MRC Human Nutrition Research; Sara Stanner, British Nutrition Foundation; Dr Sheela Reddy, Department of Health; Dr Margaret Ashwell, FSA Programme Adviser; Dr Alison Tedstone, FSA; Rachel Elsom, FSA; Mamta Singh, FSA; Cheryl White, FSA.

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