Iron: Nutrition's Two-Edged Sword

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The paradoxes of iron

Iron is the third most abundant of the elements of the earth's surface after silicium and oxygen. It has an atomic weight of 55.845, and with an atomic number of 26, is found among the transition metals in the Periodic Table of Elements.

Virtually no multi-cellular organism can survive and grow without iron

As expressed in the title, iron is a two-edged sword. On the one hand, it is an essential nutrient. Virtually no multi-cellular organism can survive and grow without iron. In humans, it is important in oxygen transport, oxidation-reduction reactions and host defense.[1] It is indispensable to have enough iron. On the other hand, it is a highly reactive element and the basis of all oxidation processes within living organisms. If iron is not confined, or if its oxidation reactions spiral out of control, it can produce severe damage to the organization.[2] One should not have too much iron.

Iron deficiency – failure to consume or absorb sufficient iron from the diet, or losing it through bleeding – are the routes to its nutritional deficiency. A consequence of iron deficiency is insufficient iron for the production of a normal volume of red blood cells. This results in iron deficiency anemia. Anemia prevalence in the world is estimated to be 1.32 billion people or about 25% of the world's population.[3] Not all of the anemia, however, is due to iron deficiency. International norms have been established for public health response to endemic anemia.[4] These call for targeted population-wide interventions with iron and folic acid if 40% or more of the population segment is anemic.

Iron excess – a genetic disease, hemochromatosis – results from a failure of the intestine to control iron absorption. Hemochromatosis produces tissue destruction and death if not detected and treated. Other iron-overload conditions, such as nutritional hemosiderosis, related in part to diet and in part to genetic predisposition, are known.[5] Negative aspects of excess accumulation of iron in the body, only slightly above the normative range, have only recently been recognized, but have been enumerated by Schümann and co-workers.[2]

"Did the 'Iron Age' end in Pemba?"

Then the aforementioned public health norm was applied to children aged six to 36 months on the Zanzibari island of Pemba off the coast of mainland Tanzania, an area of intensive transmission of *Falciparum* malaria, in a field trial of efficacy and safety.[6] The iron components of the trial were halted early, stopping randomized assignment to the recommended dose of 12 mg of iron and 50 µg of folic acid daily, when monitoring of the data showed excess mortality and hospitalization in the children receiving iron, especially among those who were not anemic. In response to these findings, and the consternation in the international public health community, Schümann and Christ[7] commented on the current status of policies for iron intervention in an essay entitled: "Did the 'Iron Age' end in Pemba?".

Recent iron research at CeSSIAM

One wing of the recent research at the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM) addresses the issues raised around the dark side and the bright side of the nutrient iron. This narrative will use three examples from our ongoing work, some of it yet to be published, to

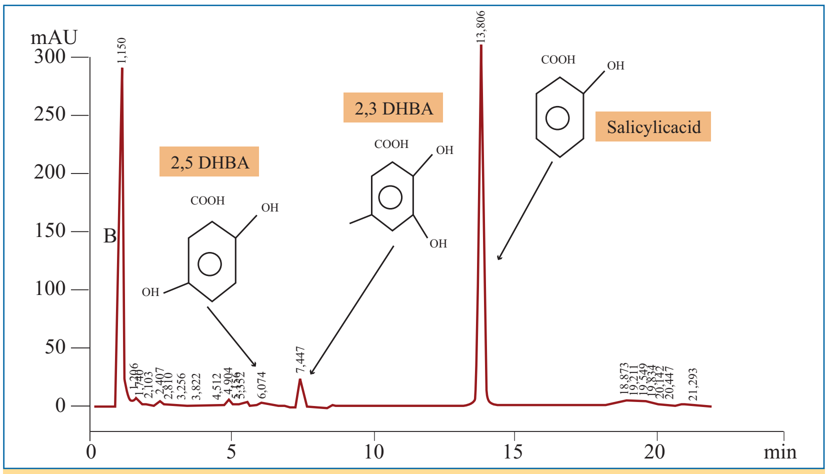

Figure 1: Chromatogram of hydroxylated products of salicylic acid, derived from *in situ* free radical attacks.

demonstrate how elements of basic and applied science blend to address a relevant problem in human health and nutrition.

Demonstrating Iron-Induced Loss of Fecal Free-Radical Suppression and a Manner to Restore: This has been the work of Monica Orozco of our group in collaboration with the Technische Universität Munich (Klaus Schümann) and the University of Manitoba (James Friel). The central question relates to the provocation of free-radical formation within the fecal stream by oral iron supplements; 120 mg of iron as ferrous sulfate is a commonly used dose given to pregnant women daily. Monica Orozco first perfected a method to determine the amount of anti-oxidant capacity in stool to buffer the generation of reactive oxygen species (ROS), which measures free-radical adducts from salicylic acid **(Figure 1)**.[8,9]

In initial metabolic studies in healthy male volunteers, six consecutive days of oral dosing with 120 mg of iron as ferrous sulfate were shown to produce a significant increase in the ROS formed *in vivo* in iron-laden stools **(Table 1)**. Our first attempt to mitigate the loss of fecal buffering capacity was to administer natural antioxidants along with the 120 mg of iron. The supplement preparation chosen was an extract of the oil palm plant (*Elaeis*) with high concentrations of α- and β-carotenes and a modest amount of tocotrienols. At both doses administered **(Table 1)**, there was a significant reduction in ROS production compared to the iron treatment alone. This has been interpreted as a restoration of the iron-induced loss of fecal buffering capacity by the exogenous antioxidant compounds in the supplement.

Quantifying Post-Oral-Iron Rise of Non-Transferrin-Bound-Iron (NTBI) and Iron Compounds that Mitigat: The mechanism by which the adverse effects of iron treatment on non-anemic children is mediated is not known. Among the speculations, however, is that a form of "free" (unbound) circulating iron, so-called "non-transferrin-bound iron" (NTBI) is involved.[10]

The World Health Organization (WHO) Lyon Consultancy warned against oral supplements or home-fortificant powders in the amount of 12.5 mg of iron, but approved the consumption of iron-fortified foods.[11] German graduate student Sylvia Kroll[12] from the Technische Universität Munich assisted Maria Eugenia Romero-Abal and they showed that the ingestion of a bolus dose of iron as ferrous sulfate at 0, 15, 30, 60, 120 and 240 mg led to an increase in circulating NTBI proportional to the increase in plasma iron in iron-replete male volunteers. Led by Maria Eugenia Romero-Abal in the metabolic study collections and Monica Orozco in the analytical laboratory, a comparison of the circulating iron and NTBI responses with ferrous sulfate, sodium ferric ethylene diamine tetra-acetate (NaFeEDTA) and iron polymaltose showed that the latter was absorbed more slowly and had reduced uptake of its iron component into the blood.

Table 1: The concentration of total hydroxylated products in fecal samples of experimental subjects according to metabolic treatment phase.

Treatment Phase	Baseline	Fe in oil	Low-dose mixed antioxidants	High-dose mixed antioxidants
Total hydroxylated products (mg/mL)	0.27 ± 0.02	0.31 ± 0.02	0.27 ± 0.03	0.27 ± 0.04

Achieving a Non-Invasive Method for Screening for Anemia in Populations of the Highlands: The current recommendations of WHO for public health iron intervention in areas of intense malarial transmission were elaborated at a consultancy in Lyon, France.[11] A specific recommendation emerged: "Universal iron supplementation for children under the age of two years is not recommended in malaria endemic areas … Prior screening to identify iron-deficient children should be a necessary component of any such intervention." The problem in implementing the screening component of this guideline is that the standard approaches for detecting iron deficiency or anemia under field conditions – fluorescent spectrometry on a drop of capillary blood[13] and cuvette-based photometry on capillary blood[14] – involve cost, culture, safety and validity. Both techniques require investment in a portable device and have reagents and disposable items with a finite and renewable operating cost. They require the obtaining of capillary blood samples, often drops of blood from a finger tip. Blood sampling is problematic in rural settings because it is painful, certain cultures have resistance to blood taking, and in the era of HIV and other blood-borne viruses, a finite risk for transmission to handlers is present. At least for the HemoCue capillary-blood hemoglobin meter, it has been established that sensitivity is limited.

Palor is the sign of anemia.

Sensitivity and specificity of the Rad-87 was poor at all four of the cut-off levels.

It would obviously be ideal if an accurate method requiring no blood extraction could be mobilized to address the screening mandate of the Lyon Consultancy.[11] Rainer Gross and a team of investigators in Indonesia, with the backing of General Electric in Germany, were the first to design, explore and publish on Erlanger Photometer (EMPHO).[15] The Microvision Co used the visualization of the microcirculation of the sublingual vasculature in the mouth to devise an algorithm for non-invasive screening.[16,17] An instrument designed for use in operating rooms for interoperative monitoring of systemic oxygenation and blood loss, the Rad-87™ with Rainbow Set technology (Masimo, Irvine, CA, USA), was shown to have high diagnostic reliability in studies in hospitalized children in Southampton, UK.[18]

A prototype of a similar apparatus, called Haemospect® (MBR Optical Systems, Wuppertal, Germany), has been tested, along with the Rad-87, in field settings in the highlands (men) and lowlands (pregnant women) in Guatemala, in order to get the widest possible spectrum of Hb concentrations. The WHO[3] defines the cut-off criterion for the diagnosis of anemia at a sea level altitude differently, depending on the population of interest:

- <11.0 g/dL for children 0 to 5 years and pregnant women;
- <11.5 g/dL for children aged 5 to 12 years;
- <12.0 g/dL for children aged 12 to 15 years and non-pregnant adult women;
- <13.0 g/dL for adult men.

Sensitivity and specificity of the Rad-87, which measures over the nail bed of the finger, was poor at all four of the cut-off levels. The measurement on the forearm with the Haemospect® was poor at <11.0 g/dL (sensitivity = 58%; specificity = 96%). However, at the next three relevant cut-off points, the diagnostic improvement was remarkable: <11.5 g/dL (sensitivity = 93%; specificity = 93%); <12.0% (sensitivity = 100%; specificity = 92%); and <13.0% (sensitivity = 97%; specificity = 97%). The application of the Haemospect® sensor to the skin on the palm of the hand had almost the same pattern. The Altman-Bland regression for forearm and hand are shown in **Figure 2.** For all zones above the lowest cut-off criterion, these values compare favorably to the best sensitivity – specificity pairing for whole blood versus capillary blood in studies by Morris et al[19] of 80% and 95% and by Neufeld et al[20] of 84% and 93%.

The residual problem of the non-invasive measurement would be that of cost, as no blood would be involved and engineering would be expected to resolve a sensitivity and specificity at least as good as the blood-based techniques.

The way forward

In each of the areas of observation there are obvious next steps to pursue. In the case of the quest for the

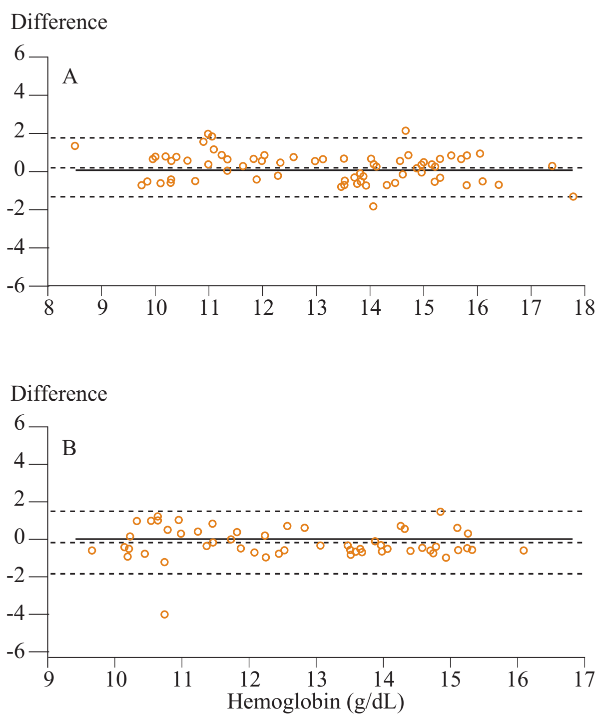

Figure 2: Altman-Bland regressions of the difference between the whole blood Hb concentration measurement using HemoCue and the digital Hb reading from the Haemospect®. **Panel A** represents placement of the probe in the palm of the hand and **Panel B** represents placement of the probe on the forearm.

mitigation of the oxidation and free-radical formation in the digestive tract associated with ingestion of therapeutic or prophylactic doses of oral iron, we need to separate whether carotene or tocotrienols are the more potent antioxidant. We need to encounter a practical dosage of antioxidants – alone or in combination – suitable for routine companionship of oral iron doses. With respect to the mitigation of free iron rises in the blood following ingestion of therapeutic or prophylactic doses of oral iron, we have proof of principle for "slow acting" iron compounds producing a lower NTBI response, we must therefore find the locations and opportunities to treat iron deficient individuals in malarial zones with the alternative formulations of oral iron. Finally, until a safe and effective iron dosing regime suitable for indiscriminant universal mass fortification becomes available, the mandate of the WHO for screening the population of malarial areas remains the most prudent course for protecting the iron-sufficient segment of the population and to eliminate exposure to individuals with normal hematological status.

The current devices need improved engineering and software to be accurate into the range for anemia in pregnant women and young children living in lowland areas. This is important because malaria is primarily a low altitude disease. However, in highland populations such as those in Guatemala, throughout the Andean region, in central South Africa, and in the Himalayan foothills, where anemia occurs at higher Hb concentrations, the investigative application of this apparatus seems to be an immediate opportunity.

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