IRON NUTRITION IN MAN: GLOBAL PERSPECTIVES ON IRON DEFICIENCY AND MALNUTRITION

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Summary

Iron is one of the most critical nutrition needs as it is difficult to cover in most diets in humans. This is indicated by the fact that it seems to be the only nutrient deficiency that presents a significant public health problem in industrialised as well as in low-income countries. However, iron deficiency is caused not only by too low an intake, but also as a result of increased iron requirement due to physiological variables or clinical problems. The fact that the dietary intake of iron does not cover the actual requirement can be due to low bioavailability, as well as secondarily to malnutrition in general, which affects the absorption and transport of iron within the body. The relative impact of iron's interaction with other micronutrients and vitamins also has to be taken into consideration.

Interestingly, poor dietary quality rather than the absolute iron intake in low income countries seems to be the key determinant of impaired iron status. Sometimes the iron

intake even exceeds that in populations of industrialised countries. The interaction of all enhancers, e.g., ascorbic acid and meat, as well as inhibitors, such as bran, polyphenols, egg yolk, soy products, calcium, and phytic acid, is what determines the bioavailability of non-haem iron in the meal. Dietary composition seems to be particularly important when iron reserves are low, or in the presence of iron deficiency. The development of anaemia as a result of iron deficiency, secondary to iron stress situations, is furthermore dependent on the iron balance in the host. With respect to the dietary intake of iron, other products in the food consumed as well as prior treatment of the product (e.g., heat treatment, processing) may also influence the bioavailability. Despite all efforts to counteract iron deficiency, this still represents one of the dominant micronutrient problems in global nutrition perspectives. This indicates that there is no simple solution to the problem and the mere fact that iron deficiency still occurs in affluent societies with a mixed diet speaks for itself: that a more holistic view on the total dietary composition and the role of enhancers and inhibitors is needed.

1. Introduction

It has been estimated that over 2000 million people suffer from micronutrient deficiencies, which can be prevented or corrected in most cases by eating a suitable range of foods. This has led international organisations to focus their nutrition interest on the three dominating micronutrient deficiencies: iron deficiency, vitamin A deficiency (see *Global Importance of Vitamin A Deficiency in Humans and its Relationship to Malnutrition*) and iodine deficiency (see *Global Importance of Iodine Deficiency in Humans; Practical Agricultural Approaches to Reduce Iodine Deficiency*). Thus, the plan of action from the international conference on nutrition in Rome in 1992 mentioned that "all efforts should be made to eliminate, before the millennium shift, iodine and vitamin A deficiencies and reduce substantially iron deficiency". This represented a follow up of the recommendations from the World Summit for Children in 1990 and the Montreal policy conference on micronutrient malnutrition in 1991. The Micronutrient Initiative was instituted in 1992 with the mission to facilitate the achievement of these goals by supporting effective and sustainable programs and to harmonise global activities. A combination of interventions was to be emphasised and implemented such as: promoting breastfeeding, modifying diet, food fortification and supplementation. Further information regarding the Micronutrient Initiative can be found through the internet (http://micronutrient.org).

So far, the best results have been obtained with respect to the reduction of iodine (see *Global Importance of Iodine Deficiency in Humans; Practical Agricultural Approaches to Reduce Iodine Deficiency*) and vitamin A deficiencies, while it has been much more complicated to reduce iron deficiency. On the other hand, the focus on the micronutrient deficiencies has been slightly hidden by the far more dominating global nutritional problem of food insufficiency leading to protein-energy malnutrition. This also secondarily leads to micronutrient deficiencies including iron deficiency.

2. Two Concepts of Malnutrition

Jelliffe introduced the two concepts *malnutrition plus* and *malnutrition minus* in order to illustrate that nutritional disturbances can occur as a result of too low an intake of one of more nutrients leading to deficiency diseases, but also that surplus of certain nutrients may lead to more or less toxic effects. Iron is a classical example of a nutrient that can result in both these two forms of malnutrition. That low intake leads to iron deficiency syndromes is well known. What is often forgotten, however, is that in excess, iron may act as a scavenger, leading to free radical formation under certain circumstances. Furthermore, as will be stated later, a high intake of iron may even aggravate an infection.

Golden has emphasised that there are two different types of responses to deprivation of essential single nutrients, *type I and type II*. In the classical type I deficiency, a low intake results in reduction in tissue concentration, which has an impact on metabolic pathways and results in characteristic symptoms and signs. The diagnosis is then relatively straight forward and can be based on measuring the concentration in suitable tissues, any disturbed metabolic functions, and/or the effect of replacing the nutrient using *in vitro* or *in vivo* studies on functional systems. A type II deficiency leads to a catabolism of the tissue with loss of all components. Such nutrients can be looked upon as interdependent, as re-synthesis can only take place if all components are available in adequate amounts. This also means that there is a generalised and not a specific response to a deficiency and no specific clinical syndrome related to a type II deficiency.

Iron deficiency is a typical example of type I deficiency according to Goldens classification, as deprivation can be diagnosed by the analysis of various biochemical parameters, e.g., serum iron, transferrin saturation, transferrin receptor, erythrocyte protoporphyrin and serum ferritin, as well as of functional disturbances, reduced plasma haemoglobin and reduced physical capacity.

3. Iron Deficiency - A Global Problem of Public Health Importance

Iron deficiency is a nutrient deficiency of great and general interest, as it seems to be the only nutrient deficiency of significant relevance for public health that affluent societies and low-income countries have in common. Since dietary habits and food availability are quite different in these two extreme types of communities, it indicates that iron is one of the most critical nutrition needs to be covered in most human diets. However, it may also indirectly illustrate that iron deficiency might not only be a question of iron intake *per se.* A number of factors, in addition to the dietary content of iron, can also result in iron deficiency. Thus we have to determine whether the deficiency is due to a low dietary intake of iron, *primary iron deficiency*, or represents a *secondary iron deficiency* due to an increased demand for iron.

A *primary iron deficiency* may not only be caused by a low intake, but could be due to poor dietary quality leading to low bioavailability, i.e., there are both quantitative and qualitative aspects of primary iron deficiency.

A *secondary iron deficiency* may be related to *physiological variables* as well as to various *clinical problems* and occurs secondary to various physiological and pathological conditions, when increased iron demand is not met by the dietary intake, or as a result of general malnutrition, which hampers iron turnover. The *physiological* conditions that cause an extra stress on iron balance are increased blood volume secondary to low oxygen tension at high altitudes, increase in muscle mass as a result of growth or extreme training, and menstrual losses and repeated pregnancies. The various *clinical and pathological* conditions that result in iron stress are increased blood losses secondary to surgical trauma, tumours and parasitic infestations. It may also be aggravated by malnutrition, which secondarily leads to disturbed iron metabolism. Thus, decreased transport capacity of iron within the body can occur as a result of protein depletion, e.g., decreased plasma transferrin levels is one example. Imbalances between micronutrients, such as the trace minerals copper and zinc, may also disturb iron availability and turnover in body tissues.

3.1. Definition of Various Forms of Iron Deficiency

Iron depletion refers to decreased amounts of storage iron without a decline in the amount of functional iron compounds. Decreased iron stores lead to insufficient amounts to cover iron requirements of different tissues, and including formation of haemoglobin, which will finally result in reduced haemoglobin content in red blood cells. *Iron deficiency anaemia*, however, is defined as anaemia with biochemical evidence of iron deficiency leading to inadequate supply of iron to the bone marrow. Anaemia is defined to occur when certain cut-off are passed for haemoglobin and haematocrits: these vary with age and sex. It is, however, essential to differ between iron deficiency anaemia and other causes of anaemia, i.e., folate deficiency and B_{12} deficiency

Age /sex	Haemoglobin cut-off	Haematocrit cut-off
	(g/100ml)	(%)
Children 6 mths-5 yrs	11.0	33
Children 5-11 yrs	11.5	34
Children 12-13 yrs	12.0	36
Non-pregnant women	12.0	36
Pregnant women	11.0	33
Men	13.0	39

(from WHO/UNICEF/UNU 1997)

Table 1. Cut-off values for diagnosing anaemia

3.2. Prevalence of Iron Deficiency

It has been estimated that 1 400 million people are affected by iron deficiency and that more than 700 million have iron deficiency anaemia. Thus, iron deficiency anaemia is only the tip of the iceberg and iron deficiency represents about 2 to 2.5 times the rate of anaemia (note that when malaria is not endemic or widespread, haemoglobinopathies occur). On the other hand, out of 1 600 million suffering from anaemia, more than 50 per cent are attributable to iron deficiency. Iron deficiency is much more prevalent in low-income countries than in the industrialised world, with estimates of approximately 38% in low-income countries *vs.* 8% in industrialised countries.

3.3. The Cost of Iron Deficiency

In 1992, USAID calculated that the poorest people in Bangladesh could raise their income by more than 20 percent by raising their iron status to normal. It has been estimated that US$ 3 per person invested in iron programs results in a US$ 63 increase in productivity per person per year, i.e., a 20-fold yield. In this perspective, any efforts to counteract the development of iron deficiency could also be analyzed in relation to gain in lifetime and productivity, the so-called disability adjusted life year (DALY). Likewise, they calculated that the costs in life years gained from reduction in mortality and a life free of illness and disability expressed as DALY show that iron fortification costs US$ 4 per DALY saved, and iron supplementation of pregnant women costs US$ 13 per DALY saved (see *The Economics of Plant Breeding as an Agricultural Strategy for Reducing Micronutrient Malnutrition*).

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Biographical Sketch

Leif Hambraeus was born 1936 in Stockholm, Sweden where he also got his medical training at the Caroline Institute (Bach Med in 1957, PhD in 1964, MD in 1967). He has been married since 1959 to Anna Fajerson, MD, PhD. and lives in Vaxholm outside Stockholm. He has four children, and eight grandchildren.

Since 1965, he worked at Uppsala University, affiliated to the Department of Pediatrics, Uppsala University Hospital, 1965-1971, where he established a metabolic ward. He had temporary appointments as assistant or associate professor of medical chemistry from 1965-67, and was acting head of the newly established nutrition unit, from 1967. He has been Professor of Human Nutrition at the Faculty of Medicine, Uppsala University, since 1972.

He was executive officer of the Swedish Nutrition Foundation 1973-78, and president of the Swedish National Committee of Nutrition from 1981-96. He was President of the Federation of European Nutrition Societies from 1979-83, as well as of the International Society for Research on Human Milk and Lactation from 1990-91. He has been a Member of the Royal Swedish Academy of Agricultural and Forestry Sciences since 1990, and a foreign member of the Finnish Academy of Science and Letters since 1997.

He has published more than 350 scientific articles in national and international journals. His research has been focused on energy and protein turnover in man, comprising studies on metabolic disorders in amino acid metabolism; nutritional aspects on breast milk composition as well as of dairy products and vegetable products with special relevance for global nutrition; metabolic studies on energy and protein interaction and substrate utilization and its relation to physical activity and protein intake, using stable isotope technique and direct calorimetry.

Under his leadership, the department in Uppsala has been engaged in building up an educational program on nutritional problems in low-income countries with an interdisciplinary approach for Scandinavian as well as international students, including the use of IT-technology.