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Review Article

ANAEMIA: A PUBLIC HEALTH CONCERN?

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A B S T R A C T

Anaemia is defined as insufficient haemoglobin (Hb) or red blood cells. Additional causes include other nutritional deficiencies (vitamins B-12, B-6 and A, riboflavin, and folic acid), chronic disease and inflammation, conditions that cause blood loss or haemolysis (e.g, parasitic infections such as hookworm or malaria or hemorrhage) (Domellof *et al* 2002). Nutritional anaemia is of public health concern in India. Though reduced intake of iron is a major aetiological factor, low intake or an imbalance in the consumption of other haematopoietic nutrients, their utilization; increased nutrient loss and/or demand also contribute to nutritional anaemia. In India, cereals and millets form the bulk of the dietaries and are major sources of non-haeme iron.The intake of iron is less than 50 per cent of the recommended dietary allowance (RDA) and iron density is about 8.5 mg/1000 Kcal. It is now well established that iron bioavailability from habitual Indian diets is low due to high phytate and low ascorbic acid/iron ratios. These factors determine iron bioavailability and the RDA. The other dietary factors affecting iron status are inadequate intake of folic acid and vitamins B_{12}, A, C and other vitamins of the B-complex group. Chronic low grade inflammation and infections, and malaria also contribute significantly to iron malnutrition. Food-based approaches to increase the intake of iron and other haematopoietic nutrients through dietary diversification and provision of hygienic environment are important sustainable strategies for correction of iron deficiency anaemia. This is possible if there is accessibility, availability and affordability to diversify food to enhance absorbability of iron in the general population. For the vulnerable groups food fortification and food supplementation are important alternatives that complement food-based approaches to satisfy the iron needs.

INTRODUCTION

Anaemia is the most common nutritional deficiency disorder in the world. WHO has estimated that prevalence of anaemia in developed and developing countries in pregnant women is 14 per cent in developed and 51 per cent in developing countries and 65-75 percent in India (Mayer and Tegman 1998) About one third of the global population (over 2 billion) are anaemic (WHO 2004). Anemia is one of the most common health problems in India (MOHFW 1998). The problem is much more in rural than the urban areas (WHO 1999). The high-risk groups for anemia are pregnant and lactating females and children (MOHFW 1998 & WHO 1999). Prevalence in this sub group has been found to vary from 50-90% in different parts of India (WHO 1999).

National and regional surveys indicate that the prevalence of anaemia could be as high as 74 percent in children below three years of age, 85 percent in expectant mothers and 90 percent among adolescent girls in some population groups (MOHFW 1998-99). Anaemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It occurs at all stages of the life cycle, but is more prevalent in pregnant women and young children. In 2002, iron deficiency anaemia (IDA) was considered to be among the most important contributing factors to the global burden of disease (WHO 2002).

Iron deficiency anaemia is a serious and widespread public health concern in both developing and developed countries. It affects 20-50% of the world's population and is common in young children (Saloojee and Pettifor 2001). The prevalence of Iron deficiency anaemia (IDA) is high in developing countries than in the developed countries due to poverty, inadequate diet, high incidence of communicable diseases, pregnancy/lactation and low immunity (Betonist *et al* 2005).

Anaemia in India: iron deficiency alone?

Anaemia, defined as a condition where the haemoglobin concentration is less than a defined level resulting in decreased oxygen carrying capacity of blood, is a serious public health

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problem in India affecting all segments of the population. The vulnerable groups are infants and young children, adolescent boys and girls, women of child bearing age and pregnant women (Agarwal 2006). Recent surveys conducted by the National Nutrition Monitoring Bureau (NNMB 2003) and National Family Health Survey (NFHS)-3(2007) show high prevalence of anaemia. NFHS-3 has reported anaemia prevalence of 56.2 per cent in women of 15-49 yr, 79.2 per cent among children aged 6-35 months, 57.9 per cent in pregnant women and 24.3 per cent in men aged 15-49 yr. Data obtained from NNMB 2003, NFHS-2(2000) and NFHS - 3(2007) show neither a time trend nor an appreciable decrease in anaemia prevalence. Anaemia prevalence seems to be the same in urban and rural areas, but gender differences exist at the age of 15 yr, with higher prevalence in females.

Regulation of Iron Absorption

Although the amount of iron extracted from the diet is small, the regulation of the intestinal absorption of iron is critical because humans have no physiologic pathway for excretion.
Iron obtained from food is not bound to transferrin, and there is no role for transferrin within the lumen of the intestine. Instead, the low pH of gastric effluent helps dissolve ingested iron and provides a proton-rich milieu. This facilitates enzymatic reduction of ferric iron to its ferrous form by a brush border ferrireductase.6 Divalent metal transporter 1 (DMT1; formerly called Nramp2 or DCT1) is a protein that transfers iron across the apical membrane and into the cell through a proton-coupled process. (Fleming *et al*., 1997 and Gunshin *et al*., 1997).

DMT is not specific to iron; it can transport a wide variety of divalent metal ions, including manganese, cobalt, copper, zinc, cadmium, and lead.(Gunshin *et al*., 1997).

Haem iron is taken up by a separate process that is not well characterized. Inside the absorptive enterocyte, iron has two possible fates: it may be stored as ferritin, or it may be transferred across the basolateral membrane to reach the plasma. These are notmutually exclusive, and the determining factor is probably an iron absorption "set point" that was established when the enterocyte developed from a crypt cell. This process represents an important mechanism of iron loss.
The absorption of intestinal iron is regulated in several ways. First, it can be modulated by the amount of iron recently consumed in the diet, a mechanism referred to as the dietary regulator. For several days after a dietary iron bolus, absorptive enterocytes are resistant to acquiring additional iron. This phenomenon has previously been called "mucosal block" (Nancy and Andrews 1999) This blocking action probably results from the accumulation of intracellular iron, leading the enterocyte to believe that its set-point requirements have been met. It may occur even in the presence of systemic iron deficiency.

A second regulatory mechanism also senses iron levels but responds to total body iron, rather than dietary iron. This mechanism has been termed the stores regulator. (Nancy and Andrews 1999). It is capable of changing the amount of iron absorbed to a limited extent: iron absorption is modulated by a factor of only two to three in irondeficient states as compared with iron-replete states. (Nancy and Andrews 1999) Although the molecular details of the stores regulator are not known, it probably acts at the level of crypt-cell programming, in response to the saturation of plasma transferrin with iron. Experiments in animals suggest that the levels of the apical transporter, DMT1, are altered in response to changes in body iron stores. .(Gunshin *et al*., 1997).

The third regulatory mechanism, known as the erythropoietic regulator, (Finch 1992) does not respond to iron levels at all. Rather, it modulates iron absorption in response to the requirements for erythropoiesis. The erythropoietic regulator has a greater capacity to increase iron absorption than the stores regulator. (Nancy and Andrews 1999) It is logical that the erythron should have some influence on the rate of intestinal iron absorption, since most of the body iron is used for erythropoiesis. Yet how it accomplishes this is unknown. The rythropoietic regulator probably involves a soluble signal that is carried by plasma from the bone marrow to the intestine.

Diseases of Iron Deficiency

Chlorosis, resulting from iron deficiency in adolescent girls, peaked in incidence. Although iron was not universally given to treat chlorosis, the disease disappeared as a clinical entity before World War II. However, iron deficiency remains an important public health problem today. In 1997, Looker *et al*. reported that 3 percent of American toddlers and 2 to 5 percent of American teenage girls are sufficiently iron-deficient to have anemia.(Looker *et al* 1997) More than half a billion people worldwide have adverse effects as a result of iron deficiency.

Iron-Deficiency Anaemia

The human body prioritizes the use of iron in several ways. During development, the fetus draws iron away from its mother for itself. After birth, the erythron has relative priority as compared with other tissues. Red-cell production is unperturbed until iron stores are depleted, as reflected by low serum ferritin levels. When the stores have been used up, the iron saturation of transferrin decreases and patients begin to show evidence of iron-deficient erythropoiesis. The first biochemical clues of iron deficiency are increased levels of free protoporphyrin and zinc protoporphyrin in erythrocytes. The levels of soluble transferrin receptor, a protein-cleavage product that is present in plasma, increase when the lack of iron limits the production of new red cells. Frank anemia with microcytosis is detected later. A decreased reticulocyte hemoglobin level is a useful early indicator of iron-deficient erythropoiesis and may be superior to other laboratory measures in this respect.(Brugnara *et al* 1999) The symptoms and signs of iron deficiency are partially explained by the presence of anemia. They include pallor, fatigue, poor exercise tolerance, and decreased work performance. However, there also appears to be a direct effect of iron deficiency on the central nervous system. In young children, measurable cognitive abnormalities may develop. 16 In both children and adults, pica Ñ a bizarre behavioral symptom that is highly characteristic of severe iron deficiency Ñ can develop. (Nancy and Andrews 1999) Pica is characterized by the inappropriate consumption of nonnutritive substances; it disappears with iron treatment.

Causes of iron deficiency are easy to understand when one accepts the fact that there is no physiologic pathway for iron excretion. Iron deficiency will result from any condition in which dietary iron intake does not meet the body's demands. For this reason, rapidly growing children and premenopausal

women are at highest risk. Worldwide, dietary insufficiency as a cause of iron deficiency is usually secondary to intestinal blood loss resulting from parasitosis. In such cases, dietary intake is unable to keep up with chronic losses.

Several forms of iron salt are used to treat iron deficiency. Perseverance is the cornerstone of successful treatment; it takes several months of replacement therapy to replenish body iron stores. Some patients have difficulty tolerating iron salts, because these substances tend to cause gastrointestinal distress. Liquid ironsalt preparations, given to young children, may cause permanent staining of the teeth. These problems can be circumvented by the use of an oral ironÐpolysaccharide complex. Both iron salts and the iron-polysaccharide preparation are inexpensive.

Infants and toddlers need relatively more ironfull-term infants have a generous iron endowment at birth, totaling about 75 mg per kilogram. (Nancy and Andrews 1999) Premature infants, infants of mothers with diabetes mellitus, and infants who are small for gestational age have substantially smaller iron stores than normal, fullterm infants.(AAPCN 1999) Stores are rapidly depleted, however, even in normal children, and there is little margin in iron balance.

Infants in the first year of life should contain 4 to 12 mg of iron per liter; Òlow ironÓ formulas containing less than 4 mg of iron per liter should not be given. Breast-fed infants receive adequate iron in a highly bioavailable form, and breast-feeding is recommended.

Anemia of Chronic Inflammation

Anemia of chronic inflammation, also known as anemia of chronic disease, has some features in common with iron-deficiency anemia. Iron-deficient erythropoiesis results from a defect in iron recycling. As a result, reticuloendothelial iron is plentiful in bone marrow macrophages, but this iron is not available to erythroid precursors. In patients with anemia of chronic inflammation, there appears to be a defect in the freeing of iron from macrophages, the loading of iron onto plasma transferrin, or both. Characteristic laboratory findings include low serum iron levels, low serum iron-binding capacity, increased serum ferritin, and normocytic or slightly microcytic erythrocytes. In contrast to patients with iron-deficiency anemia, those with anemia of chronic inflammation do not have elevated levels of serum transferrin receptor. (Nancy and Andrews 1999) The pathophysiology of anemia of chronic inflammation is not understood, but the condition probably evolved as a cytokine-ediated defense against microbial pathogens. It effectively leads to the withholding of iron from microbes as well as from erythroid precursors. (Jurado 1997) Mild anemia may be a relatively small price to pay for the attenuation of infection. The only effective treatment for anemia of chronic inflammation is correction of the underlying disorder.

Diseases of Iron Overload

Iron overload usually presents in one of two characteristic patterns. In cases in which erythropoiesis is normal but the plasma iron content exceeds the ironbinding capacity of transferrin (e.g., in cases of hereditary hemochromatosis), iron is deposited in parenchymal cells of the liver, the heart, and a subgroup of endocrine tissues. In contrast, when iron overload results from the increased catabolism of erythrocytes (e.g., in cases of transfusional iron overload), iron accumulates in reticuloendothelial macrophages first and only later spills over into parenchymal cells. Parenchymal iron loading is particularly dangerous, because it leads to tissue damage and fibrosis. The reticuloendothelial system is generally a safe sink for iron; reticuloendothelial macrophages keep it sequestered, even after rather large doses (e.g., after the administration of parenteral iron dextran). If left untreated, however, both forms of iron overload progress to parenchymal deposition and organ damage.

Hereditary Hemochromatosis

Classic hereditary hemochromatosis is the most prevalent monoallelic genetic disease. The majority of patients with hereditary hemochromatosis are descended from a common Celtic ancestor who lived 60 to 70 generations ago.(Ajioka *et al* 1997) They carry a unique missense mutation (C282Y) that alters a major-histocompatibility-complex class I-like protein designated HFE. (Feder *et al* 1996) On the basis of data from blood donors.

Several other polymorphisms have been found in the gene encoding the HFE protein, but their clinical significance is unclear. (Barton *et al* 1999, Mura *et al* 1999 and Wallace *et al* 1999) At least one of these mutations, H63D, is probably deleterious when it is present as the second allele in persons who are heterozygous for C282Y(Bacon *et al* 1999 and Olynyk *et al* 1999).

Patients with hemochromatosis regularly absorb two to three times as much dietary iron as normal persons. Most do not have symptoms until adulthood, although the saturation of serum transferrin is usually increased by adolescence. Hemochromatosis should be suspected when the serum transferrin saturation exceeds 50 percent in premenopausal women and 60 percent in men and postmenopausal women. Excess iron is deposited in parenchymal cells of the liver, heart, pancreas, pituitary gland, and parathyroid gland. Early symptoms are nonspecific; they include fatigue, arthralgia, erectile dysfunction, and increased skin pigmentation. As the disease progresses, tender hepatomegaly develops and leads to liver fibrosis and cirrhosis. There is an increased incidence of hepatocellular carcinoma after substantial damage to the liver has occurred. Iron deposition in the heart causes cardiomyopathy that is usually congestive but may be restrictive or associated with pericarditis and arrhythmias. Associated types of endocrinopathy include diabetes mellitus, hypopituitarism, hypogonadism, and hypoparathyroidism. Patients with hemochromatosis are more susceptible than others to infection, particularly with *Vibrio vulnificus, Listeria monocytogenes, Yersinia enterocolitica, Salmonella enteritidis* serotype typhimurium, *Klebsiella pneumoniae, Escherichia coli, Rhizopus arrhizus,* and mucor species.

The availability of a genetic tes of hemochromatosis has fueled controversy about the benefits of screening for the disease. The test is simple, and the disease is highly prevalent and treatable. However, important disadvantages must also be considered.
Therapeutic phlebotomy is safe, effective, and inexpensive. Each 450 to 500 ml of blood contains 200 to 250 mg of iron. Ideally, therapy is begun before symptoms develop, when the serum ferritin level exceeds 200 µg per liter in onpregnant, premenopausal women or 300 µg per liter in men and postmenopausal women. 53 Typically, phlebotomy is performed at a rate of 1 unit of blood per week until the patient has mild hypoferritinemia. Thereafter, it is continued as

needed to keep the serum ferritin level below 50 µg per liter. On average, men require phlebotomy three to four times per year, and women require it one to two times per year. (Barton *et al* 1998) When phlebotomy is instituted before end-stage organ damage has occurred, patients can have a normal life expectancy and quality of life. Even if begun later, phlebotomy can improve constitutional symptoms, relieve hepatomegaly and liver tenderness, and protect joints from arthritis. However, endocrine abnormalities and liver fibrosis, once they have developed, usually do not resolve.

In addition to performing phlebotomy, it is prudent to advise patients with hemochromatosis to modify their diets. They should avoid iron supplementation and restrict their intake of vitamin C, since vitamin C facilitates the absorption of iron. In addition, they should limit their consumption of red meat (a rich source of heme iron) and alcohol. It is wise for such patients to avoid raw shellfish, because several cases of fatal infection with *V. vulnificus* have been reported in patients with hemochromatosis. (Barton *et al* 1998)

Juvenile Hemochromatosis

In rare instances, iron overload develops in a pattern resembling that of hereditary hemochromatosis but at a greatly accelerated rate.

Several Italian families with multiple affected members have been particularly well characterized.(Camaschella *et al* 1999) Their disorder has been termed juvenile hemochromatosis. Perhaps because of the young age of these patients, or perhaps because of the rate of iron loading, they are more likely to present with cardiomyopathy and endocrinopathy than with severe liver disease. Patients with this disorder typically die of heart failure before their 30th birthdays. The genetic basis of juvenile hemochromatosis is unknown. The *HFE* gene has been ruled out as a possible locus, and juvenile hemochromatosis maps to human chromosome 1q. (Camaschella *et al* 1999 and Roctto *et al* 1999) It is reasonable to speculate that the product of the juvenile hemochromatosis gene participates in the same regulatory pathway as the *HFE* gene.

Neonatal Hemochromatosis

Neonatal hemochromatosis is a fulminant isease characterized by massive hepatic iron loading and liver failure in the perinatal period.69 Like other iron-overload disorders, neonatal hemochromatosis is characterized by the accumulation of iron in the myocardium and pancreatic acinar cells. (Nancy and Andrews 1999) The pathophysiology of this disorder is poorly understood, and it is not yet known whether iron loading is the primary problem or secondary to some other insult to developing hepatocytes. (Nancy and Andrews 1999)

Transfusional Siderosis

Long-term transfusion therapy is now a routine, life-saving treatment for patients with intractable anemia resulting from thalassemia, bone marrow failure, or aggressive treatment of cancer. In many centers, it is also used for patients with serious complicationsof sickle cell disease. As discussed earlier, there is no mechanism for iron excretion. Repeated transfusion leads to rapid iron loading, because each unit of blood contains 200 to 250 mg of iron and can cause what is known as transfusional siderosis. Since this iron is derived from red cells, reticuloendothelial macrophages become iron-loaded before parenchymal tissue cells. However, in transfusional siderosis iron is ultimately deposited in the same sites as in other iron-overload disorders (hepatocytes, the myocardium, and endocrine tissues). Cardiomyopathy is more prominent in patients with transfusional iron overload than in those with hemochromatosis, probably because of rapid iron loading. The body iron burden is best determined by quantitative liver biopsy or magnetic-susceptibility measurement (Nancy and Andrews 1999); measurement of serum ferritin and magnetic resonance imaging are less accurate methods. Phlebotomy is usually not a treatment option for patients with transfusional siderosis, because of their underlying diseases. Iron overload must be treated by chelation therapy. At present, the only option that is widely available is deferoxamine administered by continuous infusion. The goal of chelation is to maintain a hepatic iron burden of less than 15 mg per gram of liver, dry weight.(Olivieri 1999) Oral chelators are under development, but to date none are as effective or safe as deferoxamine.

Dietary iron content in the aetiology of anaemia

Humans derive iron from their every day diet, predominantly from plant foods and the rest from foods of animal origin. Iron is found in food as either haem or non-haem iron. Haem iron, which makes up 40 per cent of the iron in meat, poultry, and fish, is well absorbed. Sixty per cent of the iron in animal tissue (liver) and all the iron in plants (fruits, vegetables, grains, nuts) is in the form of non-haem iron and is relatively poorly absorbed. Non-haem iron contributes about 90-95 per cent of total daily iron in Indian diets. In western countries the intake of haem iron from meat and meat products accounts for bulk of the dietary iron and the US dietary reference intakes (DRIs) are calculated on an assumption of 75 per cent haem iron consumption (DRI 2006). On the contrary, haem iron consumption is minimal in India with majority of Indians obtaining non-haem iron from cereals, pulses, vegetables and fruits17. Thus the Indian dietary is plagued by low iron content and poor absorption.

Major sources of non-haem iron

Non-haem iron in plant foods is chemically diverse, ranging from simple iron oxides and salts to more complex organic chelates such as hydroxyphosphates in phytoferritin. The relative contribution of these chemical forms from plant foods is not yet established.

Bioavailability of non-haem iron

Gastric pH and solubility

It appears that neither higher density nor intake of iron can adequately account for the observed inter-state differences in anaemia prevalence, necessitating identification of other factors. The majority of dietary non-haem iron enters the GI tract in the ferric form, which is insoluble and thus inaccessible. This needs to be converted to the ferrous form for absorption at the enterocyte. It is well known that acidic *p*H is essential and critical for iron to be in the soluble ferrous form which in turn determines its subsequent intestinal bioaccessibility. Achlorhydria has been recognized as an associated feature of iron deficiency anaemia for many years. It is, however, not known whether the extent of acid secretion in Indians is associable with the high prevalence of iron deficiency anaemia. Evidence for enhanced iron absorption in the presence of normal gastric acidity compared to cases of achlorhydria presents an interesting option (Nair & Iyengar

2009). The gastric acidity measured by different groups in Delhi, Vellore and Mumbai was compared with that reported from western countries (Table II) (Nair & Iyengar 2009). The basal acid output in normal Indians is significantly lower (~ pH 3.4) than that in western subjects (pH 2.5) (Nair & Iyengar 2009). This difference may compromise non-haem iron solubility and accessibility in Indians and can therefore be considered in the aetiology of high anaemia prevalence. It is possible that the predominantly vegetarian dietary habit of Indians has led to such an adaptation of decreased acid secretion, as it is known that the amino acid composition of protein ingested plays an important role in determining acid secretion.

Recommended dietary allowance of iron

Bioavailability of non-haem iron from commonly consumed plant based diets in India is estimated to below due an abundance of phytic acid and polyphenols coupled with lowered consumption of meat or ascorbic acid.

Recommended Dietary Allowance (RDA) for iron by age and sex.

Age/Group	Life Stage	Iron (mg/day)
Infants	0–6 months	0.27*
	7–12 months	11
Children	1–3 years	7
	4–8 years	10
Males	9–13 years	8
	14–18 years	11
	19–30 years	8
	31–50 years	8
	51–70 years	8
	>70 years	8
Females	9–13 years	8
	14–18 years	15
	19–30 years	18
	31–50 years	18
	51–70 years	8
	>70 years	8
Pregnant Women	14–18 years	27
	19–30 years	27
	31–50 years	27
Lactating Women	14–18 years	10
	19–30 years	9
	31–50 years	9

*This value is an Adequate Intake (AI) value. AI is used when there is not enough information known to set a Recommended Dietary Allowance (RDA).

Animal products and vitamin C are amply provided simultaneously and that bioavailability of meals with a similar content of iron, energy, protein, fat, etc., can vary more than ten-fold (Key *et al* 2006). Therefore to translate physiological iron requirements into recommendations for dietary iron intakes, the bioavailability of iron (*i.e*., its absorption for utilization by the body) from different diets needs to be calculated.

Iron bioavailability of the Indian diet

Iron absorption from various Indian diets carried out by chemical balance studies reported iron absorption to vary from 7-20 per cent (median-10%) (Nair & Iyengar 2009). In 1983, detailed iron absorption studies from habitual Indian diets of single staple (wheat, rice, ragi or sorghum) were performed in adult men by the extrinsic tag technique30. Mean iron absorption from single meal ranged from 0.8 to 4.5 per cent depending on the type of staple used. The extent of absorption was the lowest (0.8-0.9%) with milletbased diets, highest (4-5%) with rice-based diets and intermediate (1.7-1.9%) with wheat-based diets. Apte and Iyengar demonstrated that during pregnancy iron absorption increased from a mean of 7 to 30 and further to 33 per cent at gestational weeks 8-16, 27-32 and 36-39, respectively, using the chemical balance method. The absorption of iron was better among those with low per cent transferrin saturation than in women with high per cent transferrin saturation. As much as 58 per cent of 30 mg of dietary iron ingested per day could be absorbed by an iron deficient full term pregnant woman. However, the magnitude of the difference in iron absorption between non pregnant and pregnant Indian women is striking even when the same balance method is used.

It is important to have an accurate measure of iron content as well as its bioavailability from the Indian diet to suggest RDA. A comparison between the extrinsic tag and the chemical balance methods indicated that the latter overestimated iron absorption (Nair & Iyengar 2009). The iron content of whole day's diet ranged from 29-42 mg, providing high iron/energy ratios (8.2-13 mg/1000 K cal). However, it is known that about 1/3rd of the total iron in cereals and pulses is due to contamination, and *in vitro* availability studies carried out on contaminant iron revealed that it was essentially unabsorbable. A uniform absorption value of iron of 3 per cent for Indian men and 5 per cent for indian women from a mixed cereal-pulse vegetarian diet was considered for deriving the iron RDA (Nair & Iyengar 2009).

Other determining factors

Although it is established that the major cause of anaemia in India is nutritional iron deficiency, it is indeed difficult to prioritize cause(s) when there are confounding factors such as multiple micronutrient deficiencies and widespread low grade inflammation. However, as explained earlier, the inter-State differences in the anaemia prevalence cannot be explained based on the iron intake or density or bioavailability alone. The other factors that will have a profound influence in the aetiology of iron deficiency include (i) simultaneous presence of other micronutrient deficiencies, especially that of haematopoietic nutrients (vitamin A, B12, folic acid and riboflavin), and (ii) acute and chronic infections such as malaria, tuberculosis, and HIV/AIDS.

Haematopoietic micronutrients

Ascorbic acid is known to improve the absorption of non-haem iron by reducing ferric iron to ferrous iron thus increasing its solubility. Vitamin C status is often marginal, as major dietary sources are seasonal vegetables and fruits. Folate and vitamin B12 are necessary for erythropoiesis and the synthesis of

DNA. The intakes of green leafy vegetables, which are major sources of folate, and animal products, which are main source of vitamin B12, are meagre in India. Inadequacy in riboflavin intake (NNMB 2000) also reduces absorption and utilization of iron. Vitamin B6 is required for haem synthesis and therefore for erythropoiesis.

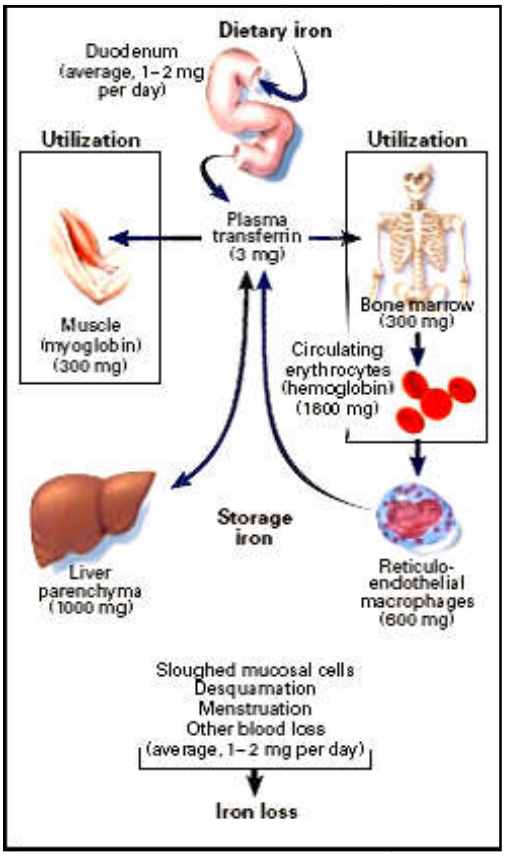
Folate nutrition in Indians

Folate, as methyl/methylene tetrahydrafolate (MTHF), acts as a coenzyme in several single carbon transfers required for the biosynthesis of purine and pyrimidines in nucleic acid synthesis. Deficiency of this vitamin decreases several biochemical functions. There are no detailed studies on folate nutritional status in the Indian population, but folate deficiency in the population is known (Krishnaswamy *et al* 2001). Poor folate content of human foetal liver was reported with the mean total liver folate showing an increase from 95 to 262 µg depending on the age (<28 to 37-40 wk) of the foetus. The birth weights of infants born to mothers who had received either 200 or 500 µg folic acid daily were higher than those born to mothers who had not received any supplements.

Vitamin B12 nutrition in Indians

There are not many studies that have specifically addressed vitamin B12 nutrition in Indians and there is no cut-off level for its deficiency. The current cut-off in the western countries is 200 pg/ml. However, the available data suggest that prevalence of B12 deficiency in children is 44 per cent (Sivakumar *et al* 2006).

Iron has the capacity to accept and donate electrons readily, interconverting between ferric (Fe2+) and ferrous (Fe3+) forms. This capability makes it a useful component of cytochromes, oxygen-binding molecules (i.e., hemoglobin and myoglobin), and many enzymes.



Iron ions circulate bound to plasma transferrin and accumulate within cells in the form of erritin. Iron protoporphyrin (heme) and iron-sulfur clusters serve as enzyme cofactors. Under normal circumstances, only trace amounts of iron exist outside these physiologic sinks, although stored iron can be mobilized for reuse. Iron balance is tenuous; both iron deficiency and iron overload are deleterious. Disorders of iron homeostasis are among the most common diseases of humans.

Adult men normally have 35 to 45 mg of iron per kilogram of body weight (Nancy and Andrews 1999). Premenopausal women have lower iron stores as a result of their recurrent blood loss through menstruation. More than two thirds of the body's iron content is incorporated into hemoglobin in developing erythroid precursors and mature red cells. Uptake of erythroid iron is highly dependent on receptor-mediated endocytosis of diferric transferrin bound to transferrin receptors.

Most of the remaining body iron is found in hepatocytes and reticuloendothelial acrophages, which serve as storage depots. The liver has first-pass access to dietary nutrients and can readily take up an amount of circulating iron that exceeds the binding capacity of plasma transferrin. Reticuloendothelial macrophages ingest senescent red cells, catabolize hemoglobin to scavenge iron, and load the iron onto transferring for reuse. This process is indispensable; the erythron alone has a daily requirement of about 20 mg of iron, (Nancy and Andrews 1999) but only 1 to 2 mg of iron normally enters the body each day through the intestine.

Sources for Iron

Iron found in animal based foods is called Heme, and plant based foods is called Non-Heme Iron when combined with protein attaches to Hemoglobin molecules in red blood cells. It carries oxygen from lungs to the rest of the body.

Iron absorption from animal foods is very efficient from 15% to 35%.Organs of all animals (Spleen, Kidney, Liver, Lung, and Heart) have a high concentration of dietary iron.

Iron absorption from plant foods may vary from 2% to 20%. Animal foods and Vitamin C increase bioavailability of iron in plant foods. Black tea and Dairy products reduce bioavailability of iron from plant foods.

Jowar, pearl millet, ragi (finger millet), soybean, red kidney beans, cowpeas, mung beans, sundakai dry (22.2 mg/100g) spinach, drumstick leaves, araikeerai, nuts, peas, cashewnut (5.81 mg/100g), dates (7.3 mg/100g), dried fruits, water melon (7.9 mg/100g), jaggery and honey. Spices and condiments like asofoetida (39.4mg/100g), turmeric(67.8mg/100g), poppy seeds(15.9mg/100g), mace (12.3 mg/100g), chillies green (4.4 mg/100g), cloves dry (11.7 mg/100g).

CONCLUSIONS

Anaemia in India is multifactorial and low iron bioavailability is a major aetiological factor. Intake of fish, fruits, nuts and oilseeds seems to have contributed to lower anaemia prevalence. Decreased gastric acid production, food matrix interactions, lack of other haemopoietic nutrients, low grade inflammation and oxidative stress are factors that contribute to iron dyshomeostasis. Low absorption reported from mixed-cereal diet is the basis for the current high RDAs and needs to be verified. A holistic approach that can simultaneously address all these issues is the lifecycle approach to anaemia

correction. A number of potential dietary sources that contain high quantities of ascorbic acid, animal products and iron absorption enhancers need to be urgently promoted including many leafy vegetables and legumes. This is possible if there is accessibility, availability and affordability to diversify food to enhance absorbability of iron in the general population. For the vulnerable groups food fortification and food supplementation are important alternatives that complement food-based approaches to satisfy the iron needs.

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