Iron content, bioavailability & factors affecting iron status of Indians

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Repeated surveys have shown that the magnitude of 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. According to the current estimates, 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. There are striking differences in the iron RDAs among the physiological groups, which need to be validated. The other dietary factors affecting iron status are inadequate intake of folic acid and vitamins B₁₂, A, C and other vitamins of the B-complex group. Chronic low grade inflammation and infections, and malaria also contribute significantly to iron malnutrition. Recent evidence of the interaction of hepcidin (iron hormone) and inflammatory stimuli on iron metabolism has opened new avenues to target iron deficiency anaemia. 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.

Key words Bioavailability - haemopoietic nutrients - intake - iron - iron status - RDA

Introduction

Iron is an essential micronutrient because it plays a vital role in oxygen transport, oxidative metabolism, cellular proliferation and many other physiological processes. It is a redox metal and participates in most of the reversible one-electron oxidation-reduction reactions by switching between the two oxidation states, ferrous and ferric. This redox activity of iron can produce free radicals responsible for cell signalling processes and iron mediated toxicity. Iron is also an essential mineral for all known pathogens, because of which many have developed complex mechanisms for iron acquisition and proliferation in an iron-restricted environment. The human body has therefore developed intricate but exquisitely controlled mechanisms to absorb, transport and store iron, thus ensuring a ready supply for cellular growth and function, but limiting its participation in reactions that produce free radicals and its availability to invading pathogens. However, anaemia is widespread in India in spite of diversity in food habits, particularly in the consumption of cereals and such tight metabolic regulation. The causality between poor dietary iron density, bioavailability and high prevalence of anaemia in our population has not been well established, as anaemia has a multi-factorial aetiology. Albeit, iron
deficiency in a population results in consequences that have serious implications and it is now recognized that even mild-to-moderate anaemia, can lead to lowered national productivity. Therefore it is important to find and address the cause(s) so as to enforce measures to reduce iron deficiency anaemia in India.

In this review, an attempt has been made to relate cereal consumption pattern, iron density and anaemia prevalence across the Indian sub-continent. Further, an update on bioavailability of iron from Indian diets and the factors that influence iron status of Indians are also included. Finally an attempt has been made to answer the question of how to meet the iron requirement.

**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 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. Recent surveys conducted by the National Nutrition Monitoring Bureau (NNMB) and National Family Health Survey (NFHS)-3 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, NFHS-2 and NFHS -3 show neither a time trend nor an appreciable decrease in anaemia prevalence (Fig. 1). 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.

Anaemia in India is not restricted to iron deficiency alone, although a few studies where the role of iron nutrition has been specifically evaluated either by biomarkers or responses to iron administration indicate that iron deficiency is the predominant cause of anaemia. In pregnant females, sTfR (serum transferrin receptor) used as a marker of tissue iron deficiency suggested low iron stores and widespread deficiency. Additionally, more than 40 - 45 per cent of preschoolers present with iron biomarkers indicating iron deficiency. In an urban slum in India, 75 per cent of the children who presented with anaemia responded to iron administration, 22 per cent of anaemic children also had biochemical vitamin B12 deficiency, 2.2 per cent had a biochemical folate deficit and 3.3 per cent were suffering from infection.

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**Fig. 1.** Time trend of anaemia prevalence in Indian women.  
*Source: Ref. 2, 5.*
A recent study carried out by the National Institute of Nutrition (NIN), Hyderabad in semi-urban school children showed evidence for the existence of multiple sub-clinical micronutrient deficiencies\textsuperscript{11}. The link between vitamin A deficiency and anaemia has been recognized for many years\textsuperscript{12}. These can potentially influence the absorption and metabolism of iron. Also, general undernutrition, haemoglobinopathies and malaria also contribute to the observed high anaemia rates\textsuperscript{13-15}. Thus based on either the prevalence or impact of iron supplementation studies there is no direct proof to demonstrate inadequate intake of iron as the only major aetiological factor of anaemia in India.

**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\textsuperscript{16}. On the contrary, haem iron consumption is minimal in India with majority of Indians obtaining non-haem iron from cereals, pulses, vegetables and fruits\textsuperscript{17}. 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.

The cereal consumption pattern in India is diverse as rice, wheat, maize are consumed to varying quantities...
According to the recent diet survey in the rural areas of 9 States, rice, wheat, and millets-ragi (Elesine coracana) and sorghum (Sorghum vulgare) are the widely consumed staples of various regions of India. The average daily intake of cereals and millets ranged from 320 to 477 g as against a recommended intake of 460 g, providing about 30-82 per cent of total dietary non-haem iron. The intake of pulses in the rural areas ranged from 18 to 37 g, and contributes to 5-10 per cent of dietary intake of iron while that from green leafy vegetables is only 2-5 per cent. Iron intake (Table I) and relative contribution of each food stuff to total iron intake (Fig. 2B) varies most widely among the States of Gujarat (23 mg), Kerala (12 mg), Karnataka (12 mg), Andhra Pradesh (8 mg) and Tamil Nadu (10 mg). In Gujarat the dietary intake of iron was the highest, arising out of consumption of bajra (8 mg Fe/100 g) as the major staple. There are differences also in the absolute amount of iron among regions, Andhra Pradesh (AP) diets with rice as the staple have lowest (7 mg/1000 Kcal) and Gujarat and Madhya Pradesh (MP) diets with bajra as the staple have the highest (16 mg/1000 Kcal) (Fig. 2C). Periodic diet surveys have shown that there is an upward trend in the iron density of Indian diets but the intake of energy has reduced over the years, implying cereal intake does not contribute to increased iron density (Fig. 3A, B). There is a good agreement in the magnitude of differences in the iron content across diets from different regions.

**Iron intake and anaemia prevalence:** Inter-state differences in iron intake and anaemia prevalence provide more insight into the complex relationship between these two. In Orissa, cereal intake is high with high anaemia prevalence while Kerala has the lowest anaemia prevalence in spite of lower cereal intake (Table I). The NNMB survey revealed that the intake of dietary iron is grossly inadequate in most of the States, meeting less than 50 per cent of RDA of males (28 mg) or females (30 mg). This deficit is highest in AP at 72 per cent and the lowest at 23 per cent in Gujarat, in adult females. These differences in iron intake are attributable to regional differences in the consumption of staple foods, especially rice and millets, as millets and wheat have relatively greater iron content when compared to rice. Although there is a marked regional difference in anaemia prevalence among these States, it is surprising to note that the extent of anaemia prevalence is not correlated with the current intake of iron, with Gujarat showing 55 per cent anaemia prevalence upon 23 mg/day iron intake and

Table I. Iron density, intake and anaemia prevalence in rural males and females

<table>
<thead>
<tr>
<th>Region</th>
<th>Iron density (mg/1000 Kcal)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iron intake* (mg/d)</td>
<td>Anaemia prevalence** (%)</td>
<td>Iron intake* (mg/d)</td>
</tr>
<tr>
<td>Kerala</td>
<td>7.1</td>
<td>13.7</td>
<td>8</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>8.2</td>
<td>12.1</td>
<td>16.5</td>
</tr>
<tr>
<td>Karnataka</td>
<td>7.7</td>
<td>15.9</td>
<td>19.1</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>4.3</td>
<td>9.4</td>
<td>23.3</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>10.4</td>
<td>18.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Gujarat</td>
<td>15.6</td>
<td>28.2</td>
<td>12</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>9.0</td>
<td>17.5</td>
<td>25.6</td>
</tr>
<tr>
<td>Orissa</td>
<td>8.5</td>
<td>17.4</td>
<td>33.9</td>
</tr>
<tr>
<td>West Bengal</td>
<td>7.1</td>
<td>16.2</td>
<td>32.3</td>
</tr>
<tr>
<td>India</td>
<td>8.5</td>
<td>16.8</td>
<td>24.2</td>
</tr>
</tbody>
</table>

*Iron intake among males/females 16 yr and above, **Prevalence of anaemia in males / females of 15-49 yr

Source: Ref. 2, 17.

**Fig. 3.** Time trends in (A) iron and (B) energy consumption.

(A) Source: Ref. 17, 58, 59; (B) Source: Ref. 60.
Kerala showing only 33 per cent anaemia prevalence upon 11 mg/day iron intake (Table I).

A similar scenario of no correlation emerges with iron density. The data also suggest that the average iron density of an Indian diet is not more than 8.5 mg/1000 Kcal, with the lowest density of 4.3 and the highest of 15.6 mg/1000 Kcal in the States of AP and Gujarat, respectively (Table I, Fig. 2C). Despite a lower iron density of 7.1 mg/1000Kcal only, anaemia prevalence in Kerala is distinctly lower (8% adult males, 32.8% adult females) compared to other States. Rice is the major staple in south Indian States but this cannot account for the observed differences as the other States of AP and Tamil Nadu (TN) have anaemia prevalence above 50 per cent, which is comparable to Gujarat where wheat and millets are the main staples.

**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 pH 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 associated 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.

The gastric acidity measured by different groups in Delhi, Vellore and Mumbai was compared with that reported from western countries (Table II). The basal acid output in normal Indians is significantly lower (∼pH 3.4) than that in western subjects (pH 2.5). 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. It would also be important to correlate Helicobacter pylori infection in Indians on gastric acid secretion and iron absorption, as these have been shown to influence iron absorption in Bangladeshi children.

**Food matrix:** It is very well known that the food matrix can influence iron solubility in the gastric milieu before it reaches the absorptive surface of the intestinal mucosa as numerous dietary factors determine the oxidation state of iron, especially from a typical Indian diet. Thus the possibility of food matrix effect on non-haem iron solubility is important. In an attempt to evaluate the impact of food matrix, in vitro non-haem iron solubility from typical Indian composite diets of Andhra Pradesh, West Bengal, Madhya Pradesh and Gujarat (based on NNMB diet survey, 2001) was carried out. Role of various dietary components in modulating solubility of iron was studied and iron content, iron density, phytate and phytate density showed significant correlation.

Iron and phytate content and density were negatively correlated to iron availability. In vitro solubility of iron from these meals decreased from 7.9 to 1.52 per cent as phytate content increased from 0.3-1.3 g/d (Fig. 4A). Further, diets with rice (low in iron and phytates) as staple had better availability compared to diets with Bajra (high in iron, phytate) as staple. Thus adequate iron availability can be achieved principally by minimizing inhibitors (phytates, tannins) and enhancing promoters (ascorbic acid, meat/fish).

Though the essentiality of ascorbic acid for efficient absorption of dietary non-haem iron is generally accepted, the intake is very low in Indian diets. For example, intake of ascorbic acid has been shown to be about 40 mg in all the States which is considered  

<table>
<thead>
<tr>
<th>Table II. Comparison of basal acid output in different populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal acid output</strong></td>
</tr>
<tr>
<td><strong>Control</strong></td>
</tr>
<tr>
<td>Delhi</td>
</tr>
<tr>
<td>Vellore (Ganguli et al, 1962)</td>
</tr>
<tr>
<td>Bombay (Vakil and Mulekar, 1963)</td>
</tr>
<tr>
<td>Edinburgh (Bruce et al, 1959)</td>
</tr>
<tr>
<td>Glasgow (Kay, 1953)</td>
</tr>
<tr>
<td>Philadelphia (Marks and Shay, cited by Marks, 1961)</td>
</tr>
</tbody>
</table>

*Mean values expressed in mEq. HCl per hour
Source: Ref. 19.
sufficient for enhancing iron uptake. It should, however, be borne in mind that the ascorbic content derived from the Nutritive Value of Indian Foods\textsuperscript{23} is for uncooked food, the content of which, upon cooking may be negligible due to the thermal instability of ascorbic acid. Thus, only observable difference in diet patterns among the above mentioned four states is the increased intake of fish, nuts and oilseeds, in Kerala (Fig. 2B), which could have contributed to increased solubility of iron resulting in the lower anaemia prevalence. Inadequate consumption of above these food groups can lead to reduced intake of other haematopoietic nutrients, vitamin A, beta carotene (nuts and oil seeds), riboflavin and folic acid, further accentuating anaemia.

Iron density of plant foods can be increased either by chemical fortification or by biofortification. In animals and plant tissues, the major iron storage protein is ferritin. Therefore, targeting ferritin iron in staple crops through conventional plant breeding technique(s), known as biofortification, is an emerging strategy. However, the bioavailability of iron content so enhanced is as yet not known and the issue of ferritin iron bioavailability is still very controversial. Studies have shown that ferritin iron from plant sources are absorbed to an extent similar to that of ferrous sulphate\textsuperscript{24-26}. We tested bioavailability of iron from pea ferritin using the Caco-2 cell line, with ferrous sulphate as positive control\textsuperscript{24}. Iron bioavailability from pea ferritin was modulated by the concomitant presence of dietary factors such as phytic and ascorbic acid, and gastric pH, suggesting it was similar in solubility and bioaccessibility to ferrous sulphate (Fig. 5). Therefore, it is essential that all strategies be aimed at simultaneously improving endogenous non-haem iron absorption enhancers in plant foods, rather than just increasing iron content or density.

**Recommended dietary allowance of iron**

Bioavailability of non-haem iron from commonly consumed plant based diets in India is estimated to be low due an abundance of phytic acid and polyphenols coupled with lowered consumption of meat or ascorbic acid. It is thus believed that plant-food based diet

![Graph](image1)

**Fig. 4.** Relationship between iron availability (A) and phytate density (B) of Indian diets. Phytate and iron content of a day’s composite diet was determined by chemical analyses and correlated with in vitro iron availability. *Source:* Ref. 22.

![Graph](image2)

**Fig. 5.** Ferritin response as a surrogate marker of pea ferritin iron bioavailability in Caco-2 cells. Bars that do not share a common superscript are significantly different at $P<0.05$. *Source:* Ref. 24.
(vegan diet) might predispose to developing iron deficiency anaemia. However, surveys in vegans have found that iron deficiency anaemia is no more common in them than among the general population, although vegans tend to have lower iron stores\textsuperscript{27,28}. The reason for the adequate iron status of many vegans may be that commonly eaten vegan foods are high in iron. In fact, the iron density (mg/1000 Kcal) of vegan foods is superior to animal-derived foods and vegan diets are high in vitamin C\textsuperscript{27,28}. Thus commonly eaten combinations, such as pulses and citrus fruits result in enhanced iron absorption and it is easy to obtain iron on a vegan diet that would meet the RDA for iron. Studies have shown that absorption rates can rise significantly from less than 5 per cent to more than 15 per cent if 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\textsuperscript{27,28}. Therefore to translate physiological iron requirements into recommendations for dietary iron intakes, the bioavailability of iron (\textit{i.e.}, its absorption for utilization by the body) from different diets needs to be calculated.

\textbf{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\%)\textsuperscript{29}. 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 technique\textsuperscript{30}. 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 millet-based diets, highest (4-5\%) with rice-based diets and intermediate (1.7-1.9\%) with wheat-based diets. Apte and Iyengar\textsuperscript{31} 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\textsuperscript{32}. The iron content of whole day’s diet ranged from 29-42 mg, providing high iron/energy ratios (8.2-13 mg/1000 Kcal). However, it is known that about 1/3\textsuperscript{rd} of the total iron in cereals and pulses is due to contamination, and \textit{in vitro} availability studies carried out on contaminant iron revealed that it was essentially unabsorbable\textsuperscript{33}. 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\textsuperscript{30,34}. RDA of iron (Table III)\textsuperscript{34} suggested earlier now appear to be unrealistic for the following reasons:

(i) The fact that the diets should provide an average of 14.2 mg of iron/1,000 Kcal (range 8.8-21) with lowest iron density recommended for children 1-6 yr and adult males and the highest for 7-18 yr boys.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Iron (mg/d)</th>
<th>Mean Energy (Kcal/d)</th>
<th>Iron mg/1000 Kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>12</td>
<td>108/Kg</td>
<td>8.8</td>
</tr>
<tr>
<td>4-6</td>
<td>18</td>
<td>98/Kg</td>
<td>9.8</td>
</tr>
<tr>
<td>7-9</td>
<td>26</td>
<td>1,240</td>
<td>21.0</td>
</tr>
<tr>
<td>Boy</td>
<td>10-12</td>
<td>34</td>
<td>1,690</td>
</tr>
<tr>
<td>Girl</td>
<td>10-12</td>
<td>19</td>
<td>1,950</td>
</tr>
<tr>
<td>Boy</td>
<td>13-15</td>
<td>41</td>
<td>2,190</td>
</tr>
<tr>
<td>Girl</td>
<td>13-15</td>
<td>28</td>
<td>1,970</td>
</tr>
<tr>
<td>Boy</td>
<td>16-18</td>
<td>50</td>
<td>2,450</td>
</tr>
<tr>
<td>Girl</td>
<td>16-18</td>
<td>30</td>
<td>2,060</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;18</td>
<td>28</td>
<td>3,030</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;18</td>
<td>30</td>
<td>2,340</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>38</td>
<td>2,640</td>
<td>14.4</td>
</tr>
<tr>
<td>Lactating women</td>
<td>30</td>
<td>2,820</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Computed based on absorption rates of 3 per cent for males, 5 per cent for females

\textit{Source}: Ref. 34
(ii) Even if an iron density of 10.8 mg/1,000 Kcal is assumed for all socio-economic groups and age/sex categories, very few Indians would satisfy RDAs for iron and energy with the present patterns of food consumption.

These current considerations make it essentially impossible for the Indian population to meet the iron requirements by normal diet alone.

A comparison of Indian and US iron RDA (Fig. 6) reveals that the US recommendations are 2-3 times lower than the Indian RDA. This difference is due to the higher bioavailability of iron in the US diet mainly attributable to increased ascorbic acid content and haem iron consumption. This magnitude of difference in RDA in itself is cause for concern as physiological requirements for the different age/sex categories do not vary to this extent across populations. This implies that enhancing bioavailability rather than density or content is of paramount importance for addressing iron deficiency anaemia in India.

*Realistic estimate of Indian iron RDA:* The iron density of Indian diet is around 8.5 mg/1000 Kcal based on diet survey records and is around 9 mg/1000 Kcal based on chemical analysis, which is lower than previously estimated (14.2 mg/1000 Kcal). A more recent iron absorption study was carried out using state-of-the-art stable isotopes in normal and iron deficient women consuming a single rice-based meal containing a total of 4.3 mg iron. The mean fractional absorption in iron-deficient subjects was 17.5 and 7.3 per cent in normal women, which is greater than absorption values (5%) used earlier for calculating iron RDA of for adult women. Considering the fact that iron absorption is inversely related to body iron stores and that

### Table IV. Dietary iron absorption (%) from habitual Indian diets in different physiological groups

<table>
<thead>
<tr>
<th>Physiological groups</th>
<th>Rice based diet</th>
<th>Mixed cereal diet</th>
<th>Wheat/millet diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Adolescent male</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Adolescent female</td>
<td>8.3</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Adult male</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Adult female</td>
<td>8</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>13.3</td>
<td>8</td>
<td>5.3</td>
</tr>
<tr>
<td>Post menopausal</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Anaemic male</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Anaemic female</td>
<td>16.7</td>
<td>10</td>
<td>6.7</td>
</tr>
<tr>
<td>Adult female</td>
<td>7.3</td>
<td>4.5</td>
<td>3**</td>
</tr>
<tr>
<td>Anaemic female</td>
<td>17.5</td>
<td>10.2</td>
<td>7**</td>
</tr>
</tbody>
</table>

*60 per cent of rice based diet; **40 per cent of rice based diet

*Source:* Ref. 34, 36

### Table V. Recommended intakes for iron from meals with bioavailability 5-10 per cent

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>RDA mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>6**</td>
</tr>
<tr>
<td>7-9</td>
<td>9**</td>
</tr>
<tr>
<td>Males 10-18</td>
<td>19 (10-14 yr)*</td>
</tr>
<tr>
<td></td>
<td>20 (15-18 yr)*</td>
</tr>
<tr>
<td>Females 10-18</td>
<td>17 (10-14 yr)**</td>
</tr>
<tr>
<td></td>
<td>18 (15-18 yr)**</td>
</tr>
<tr>
<td>Males 19+</td>
<td>17**</td>
</tr>
<tr>
<td>19-50 Adult female</td>
<td>16**</td>
</tr>
</tbody>
</table>

Pregnancy: It is recommended that iron supplements of 100 mg iron be given to all pregnant women during the second half of pregnancy are adequate. In anemic women higher doses are usually required.

Lactation: 15

Iron absorption can be significantly enhanced when each meal contains a minimum of 25 mg of vitamin C, assuming three meals per day. This is especially true if there are iron absorption inhibitors in the diet such as phytate or tannins; *5 per cent absorption; **10 per cent absorption

*Source:* Ref. 34

Indians have reduced iron stores compared to their peers in developed world, a realistic estimate of iron absorption would be 5 per cent for adult male and 10 per cent for adult female (Table IV). These figures are in agreement with the recommendations of WHO/FAO, which for didactic reasons, lists three bio-availability levels of 5, 10, and 15 per cent. According to these recommendations, for developing countries, it may be realistic to use figures of 5 and 10 per cent and in populations consuming more Western-type diets, two levels would be adequate - 12 and 15 per cent - mainly depending on meat intake. When the bioavailability of iron decreases to 10 per cent, mean iron stores are reduced to about 25 mg and about 40-50 per cent of women consuming this diet would have no iron stores. Those consuming diets with an iron bioavailability of 5 per cent have no iron stores and they are iron deficient. Based on the above considerations the RDA of iron is derived (Table V).

*Lifecycle approach:* Iron requirements are least in adult men and post-menopausal women and highest in the second and third trimesters of pregnancy and in the rapidly growing infant between 6 and 18 months of age (Fig. 7). Many studies have established the relationship between maternal iron status, foetal iron stores and birth weight. Iyengar and Apte showed that foetal body weight is directly correlated to total iron, reflecting the essentiality of iron during foetal...
development. The next high risk period for nutritional iron deficiency is the adolescent growth spurt and the onset of menstruation in girls. The needs of women of childbearing age are much higher than those of men, but quite variable because of the wide range in monthly menstrual blood loss, and may need to absorb as much as 2.5 mg each day to replenish losses. In tune with these physiological needs, the government has recently reviewed the NNACP (National Nutritional Anaemia Control Programme) to include all the vulnerable groups, known as the ‘lifecycle approach’\(^{39}\). This approach covers all physiological groups except adolescent boys and adult men. The amount of dietary iron absorbed is predominantly determined by physiological need which increases when body stores are depleted and decreases as iron stores are replenished.

**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, \(B_{12}\), 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 \(B_{12}\) 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 \(B_{12}\) are meagre in India. Inadequacy in riboflavin intake\(^{21}\) also reduces absorption and utilization of iron. Vitamin \(B_{6}\) is required for haem synthesis and therefore for erythropoiesis. Recent studies\(^{11,17,40}\) have indicated that there are other deficiencies that are currently widespread but not recognized. For example, dietary intake surveys show that intake of all the key micronutrients is low\(^{21}\). Sub-clinical deficiencies of riboflavin, pyridoxine and folic acid in pregnant women and children have been reported\(^{40}\). A study carried out in apparently normal healthy children also revealed high prevalence of sub-clinical folate, vitamins \(B_{6}, B_{2}, C, B_{12}, D\) and \(B_{1}\) deficiencies\(^{41}\).

**Folate nutrition in Indians:** Folate, as methyl/methylene tetrahydrofolate (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\(^{41}\). Poor folate content of human foetal liver was reported with the mean total liver folate showing an increase from 95 to 262 \(\mu g\) depending on the age (<28 to 37-40 wk) of the foetus\(^{42}\). Studies conducted in pregnant women also suggested poor folate status based on RBC folate levels and deficiency ranged from 40.5-53.3 per cent during different gestational periods\(^{33,44}\). Supplementation of folic acid was shown to increase the RBC folate, and in women who did not receive folic acid supplements, the levels decreased from 329 ± 129 nmol/l at term to 256 ± 118 nmol/l postpartum\(^{45}\). Significantly higher levels of RBC folate were observed only with 200 and 300 \(\mu g\) of folic acid supplementation; the increments were 91 and 195 nmol/l respectively. A subsequent study with 500 \(\mu g\) folic acid given with 60 mg iron showed a reduction in the per cent of small for date births (<2.5 kg) from 30 to 16 per cent\(^{43}\) and RBC folate levels were higher in infants born to mothers who received 300 \(\mu g\) of folic acid than those born to the control group. The birth weights of infants born to mothers who had received either 200 or 500 \(\mu g\) folic acid daily were higher than those born to mothers who had not received any supplements\(^{46}\). These studies

![Iron requirements in different physiological groups. Computed using daily iron and net energy requirements. Source: Ref. 34.](Image 72x565 to 292x712)
clearly indicate folate deficiency in the population, especially in the vulnerable groups.

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 cent⁴¹.

Iron metabolism in inflammation

Anaemia is also a consequence of a synergy of inflammation and insufficient bioavailable dietary iron and other haematinic nutrients. It is now widely recognized that infection is a much more important cause of anaemia than previously thought. Over and above the deficit in the intake of these haematopoietic nutrients, disease processes also reduce appetite, resulting in further iron deficit⁴⁷. With the onset of the inflammatory response, the plasma concentrations of several nutrients, including serum iron, decrease drastically. In addition serum ferritin concentration was shown to parallel the rapid rise in C reactive protein (CRP), both as part of the acute phase response.

Iron metabolism, infection and inflammation are inextricably linked. Iron deficiency per se has been shown to decrease both cell-mediated immune response and bactericidal activity of leukocytes in children⁴⁸. On the other hand, iron status is compromised in infection. The influence of malaria, mild and severe respiratory infections in young children on biomarkers of iron status has been studied and a significant decrease in haemoglobin was seen in children with varying degree of malaria while no significant changes were observed during upper respiratory tract infections (URTI) and pneumonia. Mean serum transferrin receptor levels changed in pneumonia affected children but not in children with URTI⁴⁹,⁵⁰. These results suggest that mild infection may not cause any significant disturbance in Hb or transferrin receptor, but this is not true for aggressive infections. In children with meagre body iron stores, infection tends to aggravate anaemia by blocking iron utilization. It is hypothesised that upon infection, iron is sequestered in the macrophages and hepatocytes and iron absorption decreases, thus limiting iron to the invading pathogen. This also results in decreased plasma iron levels, which if maintained, leads to iron restricted erythropoiesis and ultimately frank anaemia.

The anaemia of infection has recently been shown to be the consequence of induction of hepcidin expression, brought on by the action of the inflammatory cytokine IL-6. Hepcidin is a 25 amino acid hepatocyte-derived peptide that can be increased to up to 100-fold during infections and inflammation causing a decrease in serum iron levels⁵¹. Urinary or serum hepcidin concentrations are widely altered in anaemia of chronic infection, iron overload, iron deficiency and haemochromatosis⁵². Hepcidin controls plasma iron concentration and tissue distribution of iron by inhibiting intestinal and macrophage iron efflux. Iron per se has also been shown to modulate hepcidin levels⁵³. Thus hepcidin is now considered as the iron hormone.

Iron and oxidative stress

Multiple micronutrient deficiencies co-exist with anaemia in India. Many of these micronutrients, in addition to their role in the aetiology of anaemia, are pro- or anti-oxidant. Ascorbic acid in the presence of iron is a pro-oxidant whereas alpha tocopherol is an antioxidant that can quench OH⁻. Optimal concentration of glutathione peroxidase, a key antioxidant enzyme which also protects haemoglobin against oxidation in erythrocyte, requires selenium. However, it is difficult to assess the extent of deficiencies of these micronutrients, their contribution to iron mediated oxidative stress in the vulnerable segments of the population where iron supplementation is practiced⁵⁵. It is essential to condition the system with these micronutrients to achieve optimum impact of the lifecycle approach of iron deficiency control programme. These will not only reduce the anaemia prevalence but also reduce the oxidative stress associated with excess iron supplementation. In support of this, we have shown that preconditioning of iron deficient rats with alpha tocopherol and ascorbic acid protected against iron mediated oxidative damage⁵⁴-⁵⁶. This raises the question of whether iron deficient pregnant women are more susceptible to oxidative stress resulting from excess iron absorption, particularly when given daily pharmacological doses of iron⁵¹. The other strategies to control deleterious effects have been previously reviewed⁵⁷.

Conclusions

Anaemia in India is multifactorial and low iron bioavailability is a major aetiological factor, given the current iron density of 8.5 mg/1000 Kcal. Inter-State differences in anaemia prevalence are not correlated either with iron intake or density. Intake of fish, fruits, nuts and oilseeds seems to have contributed to lower anaemia prevalence in Kerala. 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 and need to be addressed. Low absorption reported from mixed-cereal diet is the basis for the current high RDAs and needs to be verified. Recent stable isotope studies have shown absorption rate of 10 per cent in adult females, thus reducing the RDA to 16 mg as against 30 mg. Thus the RDAs for the other groups have to be re-established. 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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