Role for Micronutrient Interactions in the Epidemiology of Micronutrient Deficiencies: Interactions of Iron, Iodine and Vitamin A

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Introduction

Iron, iodine and vitamin A are the most common micronutrient deficiencies and affect one third or more of the world's population. It is estimated that 2 billion people are anemic based on low hemoglobin (Hb) levels, that 1.9 billion have inadequate iodine nutrition based on low urinary iodine levels, and that 250 million preschool children are vitamin A-deficient based on low serum retinol concentrations [1]. The prevalence of anemia due solely to iron deficiency is less certain because anemia has several different causes including the deficiency of iron, the deficiency of other micronutrients, infections and malaria. It has been suggested, based on the findings of Asobayire et al. [2], that the prevalence of iron-deficiency anemia (IDA) can be estimated as approximately half of the prevalence of anemia per se [1], and additionally that there are a similar number of people who have iron deficiency (no iron stores) without anemia as have iron deficiency with anemia. Thus it can be estimated that about 2 billion people are iron deficient, of which about 1 billion have IDA.

It has been common practice to evaluate the epidemiology of micronutrient deficiencies separately for each micronutrient and to develop individual strategies for their prevention or treatment. Simple logic, however, would tell us that single micronutrient deficiencies rarely occur in isolation, especially in infants, children and women from the poorer socioeconomic groups in the developing world. Growing children and pregnant and lactating women have a higher requirement for all nutrients, and economically poor populations typically consume nutritionally poor diets based on cereals and legumes, with
little animal-source foods, fruits and vegetables. It is well accepted that such
diets are low in bioavailable iron and vitamin A. Low iron bioavailability is a
major factor in the etiology of iron deficiency [3], together with parasitic
infections [4] and high menstrual blood losses in women of child-bearing age
[5]. Low dietary retinol and low intake and poor bioavailability of pro-vitamin A
carotenoids are likewise the major factor in the etiology of vitamin A
deficiency [6]. Plant-based diets, however, would also be expected to be low in
zinc, riboflavin, vitamin B₆ and vitamin B₁₂, and, if little fruit and vegetables are
consumed, also low in vitamin C and folate. Deficiencies of these micro-
nutrients, although rarely measured, could also coexist with iron and vitamin A
deficiencies and, in addition, if the soils are low in iodine [7] or selenium [8],
deficiencies in iodine and selenium may also be present.

As multiple micronutrient deficiencies coexist, it is therefore possible that
a deficiency of one micronutrient influences the etiology, prevention or
treatment of another micronutrient deficiency. Table 1 shows the prevalence
data reported for iron, iodine and/or vitamin A deficiencies in the same
individual [9–17]. Clearly many interactions between micronutrients are
possible but recent attention has focused on interactions influencing the
etiology of anemia, including IDA, and interactions influencing iodine defi-
ciency. In addition to iron, low intakes of vitamin A [18], riboflavin [19], folic
acid, vitamins B₁₂, B₆ and C [20] could all influence the etiology of anemia. Similarly, in addition to low iodine intake [7] and intake of goitrogens [21],
poor iron status [12], vitamin A status [22] or selenium status [23] may
influence the etiology of iodine deficiency, and may reduce the efficacy of the
strategies used for its prevention or treatment [14, 24].

This review focuses on the possible interactions of iron and vitamin A in
the etiology of anemia and the possible interactions of iron and iodine in the
etiology of iodine deficiency.

**Interaction of Vitamin A with Iron in the Etiology of Anemia**

The link between vitamin A deficiency and anemia has been known for
many years. What is still not known is the mechanism by which vitamin A
exerts its effect. An interaction of vitamin A in iron metabolism is the most
likely explanation and several mechanisms have been proposed [25]. In
tropical countries, the high prevalence of infectious diseases might also play
a role as vitamin A deficiency can decrease immune function, due to a
modulation of hematopoiesis [26], and thus increase the anemia of infec-
tion [27].

In the classic study of Hodges et al. [28], 8 middle-aged men were fed a
combination of 3 different vitamin A-deficient diets together with mineral and
vitamin supplements for 360–770 days. The intake of all nutrients, except
vitamin A, was judged adequate. However, despite a daily intake of 18–19 mg
iron, the men developed mild anemia after about 6 months. As plasma retinol levels fell from what was described as plentiful (>30 μg/dl) to adequate (20–30 μg/dl) and on to low (<20 μg/dl), the mean Hb values fell from 15.6 to 12.9 g/dl and onto 11.9 g/dl. The anemia was not responsive to iron therapy until the subjects were repleted with vitamin A.

Cross-Sectional Studies

Despite the influence of other nutritional factors and infectious diseases on both vitamin A and iron status, many cross-sectional studies in developing countries have reported a positive correlation between serum retinol and Hb concentration. The correlation becomes more apparent with lower vitamin A status [20].

Possible Interactions of Vitamin A in Iron Metabolism

Iron metabolism can be described as a closed loop representing primarily the formation and destruction of red cells. Small amounts of iron enter this loop via the absorption of dietary iron and, in balance, an equivalent amount of iron exits in the loop as losses from blood and tissues (fig. 1). Vitamin A deficiency has been proposed to influence iron metabolism either via a decrease in erythropoiesis with less iron incorporated into red blood cells [25] or indirectly by improving immune function and decreasing the anemia of infection [26]. In addition, dietary vitamin A has been reported to increase iron absorption [29]. Proving these theories, as well as confirming the effect of vitamin A, on iron absorption has been difficult, and the exact mechanism of the vitamin A/iron interaction still remains to be established.

In rats, vitamin A deficiency reduces the incorporation of radioactive iron into erythrocytes by almost 50% [30], alters red blood cell morphology [31], produces mild anemia [32, 33], lowers plasma total iron-binding capacity and percent transferrin saturation [33–35], but not circulating transferrin concentrations [35], and causes an accumulation of iron in the liver [30, 36], spleen [30, 33, 34] and bone [33, 34]. Vitamin A deficiency in rats, in addition, appears to increase iron absorption from the gut [30, 32, 33].

Based on these studies Roodenburg et al. [34] hypothesized that vitamin A deficiency impairs erythropoiesis so that mild anemia with malformed cells develops. The abnormal erythrocytes would be broken down by the macrophages of the reticuloendothelial system at an increased rate and so help explain the accumulation of iron in the spleen. In vitro studies would indicate that retinoids influence erythropoiesis but that the influence is complex, depending on the stage of erythrocyte development [37], and may involve a direct effect on erythropoietin formation [38]. However, Roodenburg et al. [25] could find no evidence in rats that vitamin A deficiency effects erythropoiesis and speculated that iron accumulation in the spleen may be related to a reduced iron transport due to an inhibition of transferrin synthesis, although Mejia and Arroyave [35] found no decrease in circulating
**Table 1.** Epidemiological studies of anemia, iron, vitamin A and iodine deficiencies and co-occurrence

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Year</th>
<th>Location</th>
<th>Prevalence of single deficiency</th>
<th>Prevalence of multiple deficiencies</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>iron</strong></td>
<td>vitamin A</td>
<td>iodine</td>
<td>iron and vitamin A</td>
<td>iron and iodine</td>
<td>vitamin A and iodine</td>
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<tr>
<td>Infants 6–12 months (n = 98)</td>
<td>1998</td>
<td>South Africa</td>
<td>39% IDA; Hb &lt;110 g/l, SF &lt;10 μg/l</td>
<td>13% VAD; serum retinol &lt;0.7 μmol/l</td>
<td>7% ID and VAD</td>
</tr>
<tr>
<td>Children 1–5 years (n = 919)</td>
<td>1995</td>
<td>Republic of Marshall Islands</td>
<td>24% IDA; 54% ID; Hb &lt;110 g/l, SF &lt;12 μg/l</td>
<td>60% VAD; serum retinol &lt;0.7 μmol/l</td>
<td>33% ID and VAD</td>
</tr>
<tr>
<td>Children 1–5 years (n = 1,243)</td>
<td>1996</td>
<td>Honduras</td>
<td>29% anemia; Hb &lt;110 g/l</td>
<td>14% VAD; serum retinol &lt;0.7 μmol/l; 45% low vitamin A stores; serum retinol &lt;1.05 μmol/l</td>
<td>16% anemia and low vitamin A stores</td>
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<tr>
<td>Children 6–12 years (n = 419)</td>
<td>1997</td>
<td>Côte d’Ivoire</td>
<td>27% IDA; Hb &lt;110 g/l and SF &lt;12 μg/l or TIR &gt;8.5 mg/l and ZPP &gt;40 μmol/mol heme</td>
<td>45% goiter by palpation</td>
<td>19% IDA and goiter</td>
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<td>Children 6–15 years (n = 329)</td>
<td>1999</td>
<td>Côte d’Ivoire</td>
<td>17% IDA; 35% ID; Hb &lt;115 g/l, SF &lt;12 μg/l or TIR &gt;8.5 mg/l and ZPP &gt;40 μmol/mol heme</td>
<td>45% VAD; serum retinol &lt;0.7 μmol/l</td>
<td>74% goiter by ultrasound using provisional WHO/ICCIDD reference values¹</td>
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<tr>
<td>Age Group</td>
<td>Country</td>
<td>Year</td>
<td>Prevalence Rates</td>
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<tr>
<td>Children 6–15 years</td>
<td>Morocco</td>
<td>2001</td>
<td>36% IDA; 51% ID; Hb &lt;115 g/l; SF &lt;12 μg/l or TfR &gt;8.5 mg/l and ZPP &gt;40 μmol/mol heme</td>
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<td>71% goiter by ultrasound using provisional WHO/ICCIDD reference values</td>
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<td>35% IDA and goiter; 50% ID and goiter</td>
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<tr>
<td>Pregnant women 16–19 years</td>
<td>India</td>
<td>2000</td>
<td>46% anemia; Hb &lt;110 g/l; 16% night blindness</td>
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<td>15% goiter by palpation</td>
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<tr>
<td>Pregnant women 15–40 years</td>
<td>Nepal</td>
<td>1994–1997</td>
<td>64% IDA; 81% ID; Hb &lt;110 g/l; SF &lt;10 μg/l and/or ZPP &gt;70 μmol/mol heme</td>
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<td></td>
<td>54% low vitamin A stores; serum retinol &lt;1.05 μmol/l</td>
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<td></td>
<td>38% SF &lt;10 μg/l and serum retinol &lt;1.05 μmol/l</td>
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<tr>
<td>Anemic pregnant women</td>
<td>Malawi</td>
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<td>55% IDA; Hb &lt;105 g/l and SF &lt;30 μg/l</td>
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<td></td>
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<td></td>
<td>39% VAD; serum retinol &lt;1.05 μmol/l</td>
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<td></td>
<td></td>
<td>17% IDA and VAD</td>
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Hb = Hemoglobin; ID = iron deficiency; IDA = iron deficiency anemia; SF = serum ferritin; TfR = transferrin receptor; VAD = vitamin A deficiency; ZPP = zinc protoporphyrin.

transferrin concentrations in vitamin A-deficient rats. Nevertheless, it is possible that vitamin A is involved somehow in the release of iron from the spleen or the liver stores, or perhaps directly in the incorporation of iron into Hb. Some evidence for an influence of vitamin A on the mobilization of liver and spleen iron comes from the study of van Stuijvenberg et al. [39]. Children receiving an iron-fortified soup increased serum iron levels and transferrin saturation to a greater extent when plasma retinol levels were >40 µg/dl as compared to <20 µg/dl.

**Infection**

Although it seems reasonable to speculate that vitamin A enhances immunity, reduces infection and thus the anemia of infection, there are little data available to support this directly [40].

**Absorption**

Human studies investigating the influence of vitamin A on iron absorption have produced contradictory results. One group has reported an increase in iron absorption by Venezuelan subjects from iron-fortified bread meals in the presence vitamin A or β-carotene [29, 41] (fig. 2). The other group reported no effect of vitamin A on iron absorption when similar meals were fed to Swiss and Swedish students [42] and an inhibition of iron absorption when vitamin A was added to a maize meal fed to vitamin A-deficient children in the

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**Fig. 1.** Possible influence of vitamin A deficiency on iron metabolism.
Côte d'Ivoire [43]. In the same children, there was no effect on iron absorption of vitamin A 3 weeks after they had been supplemented with a high dose of vitamin A. The methods used to estimate iron absorption in all studies were similar and based on erythrocyte incorporation of either stable or radioactive isotopes. This methodology quantifies iron that is first absorbed and then incorporated into Hb. Any effect of vitamin A could be on either the absorption stage, or on the subsequent incorporation of iron into Hb, or on both the absorption and utilization.

It is difficult to explain these contradictory results. Small differences in methodology seem an unlikely explanation. It seems more probable that differences in the nutritional status of the study subjects or their disease state at the time of the absorption study could explain their different responses to dietary vitamin A. Erythropoiesis, including the incorporation of iron into Hb, can be influenced by factors other than iron and vitamin A nutrition. Riboflavin [19], folic acid, vitamin B₁₂ and vitamin B₆ status [20] can all influence red cell formation, as can chronic infections [44]. A detailed nutritional status evaluation of the study subjects from Venezuela and the Côte d'Ivoire was not made. Previous studies in the Côte d'Ivoire have reported that chronic infections, malaria, and intestinal parasites are common in school-aged children from similar populations [2]. These combined results from Venezuela, Côte d'Ivoire and Europe thus indicate the complexity of the interaction of vitamin A status, dietary vitamin A and iron metabolism and emphasize the difficulty in extrapolating results from an industrialized to a developing country, and even extrapolating from one developing country to another developing country where diet and lifestyle are different.

**Fig. 2.** Influence of vitamin A and β-carotene on iron absorption (including both iron absorption and iron incorporation into hemoglobin) from maize bread, wheat bread and rice meals [41]. Maize flour and wheat flour were fortified with 5 and 2 mg Fe, respectively, as ferrous fumarate and fed as bread with margarine and cheese. Rice was unfortified and fed with margarine.
**Interventions**

Many intervention studies have shown that vitamin A supplements, or foods fortified with vitamin A, improve blood Hb concentrations in children and pregnant or lactating women [40]. In addition, some studies have shown that dual supplementation of iron with vitamin A have a greater impact on Hb concentrations than iron alone, in both children [45] and pregnant women [18]. However, some studies have shown no significant effect of vitamin A on Hb concentrations [46], which might be expected especially if vitamin A status is adequate [47].

From these studies, it can be concluded that both vitamin A and iron are required for normal red cell production. The exact nature of the interaction, however, is not known, but vitamin A could be needed for erythropoiesis, including the incorporation of iron into Hb, and may be needed for mobilization of iron from spleen or the liver stores. Alternatively, the positive influence of vitamin A on the immune system may influence erythropoiesis via an influence on the anemia of infection. Because other nutritional factors and disease factors can influence erythropoiesis, it is not possible to generalize on the additional beneficial effect on anemia prevention or treatment of providing both iron and vitamin A. Where vitamin A nutrition is marginal and iron deficiency common, dual fortification or supplementation can be recommended. Where other micronutrients may be lacking in the diet, then multiple micronutrient fortification together with iron may be necessary to get the maximum impact on iron status.

**Interactions of Iron and Iodine Metabolism**

Extensive data from animal studies indicate that iron deficiency, with or without anemia, impairs thyroid metabolism. Weanling rats fed iron-deficient diets have significantly lower plasma triiodothyronine (T₃) and thyroxine (T₄) concentrations and blunted thyrotropin (TSH) responses compared to rats fed adequate iron [48]. Rats with iron deficiency have reduced peripheral conversion of T₄ to T₃ [49] and significantly lower hepatic 5’-deiodinase activity than controls [50]. However, a limitation to these earlier studies is the lack of pair-feeding, as some of the observed effects of anemia could be explained by reduced food intake and thus caloric restriction. A widely recognized effect of thyroid hormones is their influence over energy metabolism [51]. As food intake is reduced in anemia, the lower thyroid hormone concentration may be in part a physiologic adaptation. This has been confirmed by reduced thyroid hormone concentrations in modified fasting of rats [52].

A few studies in humans also showed that IDA decreases the thyroid hormone concentration. However, the results are not consistent. Beard et al. [53] reported a significant difference in T₃ concentration between anemic
(Hb <110 g/l) and non-anemic women although TSH was in the normal range. On the other hand, there was a nonsignificant 10% lower T3 concentration in severely anemic (Hb 75 g/l) Venezuelan subjects [54] and no difference in T3, T4 and TSH in iron-deficient anemic American women [55]. Although, in the latter study, when the women were subjected to cold exposure, T3, T4 and TSH increased to a lesser extent than in the non-anemic women.

Cross-Sectional Studies

Data from the few available cross-sectional studies, which have investigated the correlation between iodine deficiency and IDA, are equivocal. A survey in Ethiopian children found no correlation in goiter rate or thyroid hormone levels and iron status [56]. However, in severely vitamin A-deficient Ethiopian children, low levels of T3 were associated with low serum iron and low transferrin saturation [57]. A national screening in 2,917 children in Iran has reported a highly significant difference in goiter rates by palpation between children with low and normal serum ferritin (SF) levels [58]. Goiter was 3.8 times more prevalent in schoolchildren with low SF levels than in children with normal SF concentrations. Moreover, Zimmermann et al. [12] in 1997 assessed iron status and goiter rate by palpation in 419 children aged 6–15 years in two villages in western Côte d'Ivoire and found a relative risk of 1.9 (confidence interval 1.5–2.3) for goiter for children with IDA.

Possible Mechanisms of the Iodine and Iron Interaction

It is not clear how iron deficiency exerts its effects on thyroid and iodine metabolism. There are several theories in the literature as to the possible interactions of iodine and iron metabolism. These include alterations in the thyroid hormone feedback system, a reduced synthesis of thyroid hormones in the thyroid, a lower transformation of T4 to T3 in the peripheral tissue, and nonspecific alterations due to hypoxic stress (lack of oxygen). Beard et al. [59] suggest that IDA induces changes in thyroid metabolism through alterations in central nervous system control resulting in an altered feedback system. Under normal conditions, thyroid hormones inhibit the synthesis of TSH directly at the pituitary level and indirectly via a decrease in the secretion of thyrotropin-releasing hormone at the hypothalamic level.

In the periphery, the lowered [125I]T3 binding to hepatic nuclei shown in rats could also be a contributory mechanism [60]. In addition, IDA leads to a decreased hepatic 5′-deiodinase activity, which catalyzes the conversion of T4 to T3 [50, 61, 62]. The depression of 5′-deiodinase activity is greater in more severely iron-deficient anemic rats (72%) than in the less severely anemic rats (25%) [61]. Although the lowered hepatic 5′-deiodinase activity observed in iron deficiency may be at least partially attributed to low plasma T4 concentrations, normalizing plasma T4 did not normalize hepatic 5′-deiodinase activity. These observations suggest that the mechanisms that control hepatic 5′-deiodinase activity (e.g. enzyme synthesis, allosteric regulation of enzyme
activity) are directly affected by iron deficiency, regardless of thyroid hormone status [61]. According to Beard et al. [59], however, the effect of iron deficiency on either the hepatic 5′-deiodinase or the brown fat deiodinase II observed in rats is rather minimal. Moreover, using an in vitro method, outer ring deiodinase activity is not affected by either ferric or ferrous iron [63]. It should be noted that this enzyme is also selenium-dependent [23]. Presumably, in iron-deficient anemic rats, a smaller portion of T4 is converted to T3 and a larger portion is converted to reverse T3, a physiologically inactive metabolite, which indicates that iron-deficient rats are functionally hypothyroid, with a tendency toward thyroid hormone inactivation versus activation [64].

Another potential mechanism for reduced thyroid hormone concentration in IDA is impairment of thyroid peroxidase (TPO) activity. TPO is a glycosylated, heme enzyme bound to the apical membrane of the thyrocytes [65]. It plays a key role in thyroid hormone synthesis as it catalyzes the two initial steps, iodination of the thyroglobulin and coupling of the idodotyrosine residues [66]. We have recently shown that TPO activity is significantly reduced in IDA [67]. Male weanling Sprague-Dawley rats (n = 84) were assigned to 7 groups. Three groups (ID-3, ID-7, ID-11) were fed iron-deficient diets containing 3, 7 and 11 μg iron/g diet. An iron-sufficient diet was fed to 3 pair-fed groups, whereas it was consumed ad libitum by 1 control group. After 4 weeks, Hb, T3 and T4 were significantly lower in the iron-deficient groups than in the control group (p < 0.001). TPO activity (by both guaiacol and iodide assays) was markedly reduced by iron deficiency (p < 0.05). Compared to the ad libitum control group, TPO activity per total thyroid determined by the guaiacol assay in the ID-3, ID-7 and ID-11 groups was decreased by 56, 45 and 33%, respectively (p < 0.05).

Thyroid metabolism could also be impaired nonspecifically by iron deficiency through anemia and lowered oxygen transport, similar to the thyroid impairment of hypoxia found in animals [68]. Thyroid impairment was also found in chronically hypoxic children, who had not only increased levels of reverse T3, but also decreased concentrations of T4 and T3, whereas in acutely hypoxic children, mean serum T4 and T3 concentrations were not altered, but the mean serum reverse T3 concentration was significantly elevated [69]. However, in healthy subjects hypoxic stress led to marked elevations in plasma T4 and T3 within 4 h and the increased levels were maintained during the entire period of exposure [70, 71]. This indicates that in a healthy subject, hypoxia cannot entirely explain hypothyroidism associated with IDA.

**Evidence from Intervention Studies**

In a first study in 1997, Zimmermann et al. [12] investigated the effect of a 200-mg oral dose of iodine as iodized oil in non-anemic (n = 51) and iron-deficient anemic (n = 53) children with goiter in western Côte d'Ivoire.
At 15 and 30 weeks the thyroid volume was significantly reduced in the non-anemic group compared to the IDA group (p < 0.001). A clear difference in goiter prevalence was apparent at 15 and 30 weeks, when goiter rates were 62 and 64% in the IDA group and only 31 and 12% in the non-anemic group, respectively. After 30 weeks, the TSH and T4 concentrations improved significantly in the non-anemic group compared to the IDA group. Beginning at 30 weeks, the children with IDA were given 60 mg oral iron as ferrous sulfate 4 times/week for 12 weeks [72]. This resulted in an increase in Hb (±SD) from 97 ± 8 g/l at 30 weeks to 122 ± 8 g/l at 50 weeks. The change in thyroid volume, which had reached a plateau at weeks 10–30, began to fall again after iron supplementation. Consequently, goiter prevalence in the IDA group, which had remained at 62–64% from weeks 10 to 30, was reduced after iron supplementation to 31 and 20% at 50 and 65 weeks.

A randomized, double-blind, placebo-controlled trial in 5–14 years old children in Côte d’Ivoire confirmed that iron supplementation (60 mg iron/day, 4 days/week for 16 weeks) improves the efficacy of iodized salt in goitrous children with iron deficiency [24]. The mean reduction in thyroid volume in the iron-treated group was twice that in the placebo group: −22.8 ± 10.7 compared to −12.7 ± 10.1%. In a 9-month fortification trial in goitrous Moroccan children comparing dual-fortified salt containing iodine and iron with iodized salt alone [73], greater improvement in thyroid function was found in the group receiving the dual-fortified salt. The prevalence of goiter and hypothyroidism was significantly reduced in the dual-fortified salt group, compared to the iodized salt group. Overall, these results suggest that a high prevalence of iron deficiency among children in areas of endemic goiter may reduce the effectiveness of iodized salt programs and strongly support the current recommendations by the World Health Organization [74] for combined supplementation and fortification using multiple micronutrients.

**References**

Micronutrient Interactions

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Discussion

Dr. Guesry: What were the respective levels of phytic acid in the maize bread in Switzerland and Venezuela? In Switzerland flour is usually quite refined.

Dr. Hurrell: We used a maize flour from Migros, a local supermarket. The phytic acid content was found to be about 300 mg/100 g which is a fairly high phytic acid-containing maize flour and not so different from that used in Venezuela. We did not use a degermed maize flour, but if the germ is removed from maize you get a non-phytic acid-containing maize flour.

Dr. Pettifor: You showed a very small effect of vitamin A supplementation on iron status basically. Would you postulate then on whether you believe vitamin A plays as a major role? It is just one of the many aspects in the many different areas that could influence iron status.

Dr. Hurrell: The exact role of vitamin A has not been demonstrated, but one possible effect of vitamin A on iron bioavailability could be related to its influence on the incorporation of iron into the hemoglobin. During iron bioavailability studies, it is common practice to calculate iron absorption by assuming an 80% erythrocyte incorporation of absorbed iron in normal healthy individuals. This 80% value varies from 60 to 90%, so it is a rough approximation. We wondered whether the contradictory results obtained on the influence of vitamin A on iron absorption could be related to this incorporation factor being different in subjects with different vitamin A status. In the first 2 studies I presented iron absorption in a traditional way using an 80% incorporation factor. In the last study, which was recently published, Davidsson et al. [1] reported erythrocyte incorporation directly avoiding the use of an incorporation factor.
The group of Roodenburg et al. [2] made a series of rat studies about 10 years ago, and they suggested that one other major effect of vitamin A on iron metabolism might be the release or the mobilization of iron from the stores. The other possibility is that vitamin A is needed for the differentiation of the red blood cells.

Dr. Zlotkin: In your second slide on epidemiology, you showed estimated numbers on deficiencies of iodine, iron and vitamin A around the world. I was quite taken with the fact that the estimates are different depending on who is giving the lecture or whose article you have. The issue is important from an advocacy perspective because, when we go to policy makers, it is quite important that we can justify the numbers we use. How important do you think it is from an epidemiological perspective that we have some agreement on the definition of terms? For example, in your talk you didn’t define your terms at all; the terms of how we define iron deficiency. We know in West Africa, for example, that much of the anemia is not from nutritional deficiencies but from malaria. That number may be lumped in with the total of 1 billion with iron deficiency. So again my question is, how important is it that we agree on the definition of terms?

Dr. Hurrell: This is extremely important, but it is a very difficult question. The prevalence estimates I presented came from the WHO and will be published next year in the Fortification Guidelines which I have been involved in putting together. One of the main problems in preparing this document was obtaining reliable prevalence values. I can speak only for iron because that is my main area. Normally the prevalence of iron deficiency is based on hemoglobin levels. The data I presented were also based on hemoglobin values and, in addition, we assumed that half of the people who were anemic had iron-deficiency anemia (IDA) and half had anemia of other causes. According to the WHO, there are 2 billion people who are anemic worldwide. The estimation that 50% of the anemic subjects have IDA was an average based on African studies which reported that 80% of the anemia in children was due to iron deficiency and some 30–40% in women. By taking a 50% average value we came up with 1 billion people worldwide with IDA. Again in some African studies about the same number of people have IDA as have iron deficiency without IDA. So the prevalence of iron deficiency without IDA is about the same as the prevalence of iron deficiency with IDA, so we get back to the 2 billion people with iron deficiency, half with anemia and half without. Recently we have been doing efficacy studies and needed cohorts of children or women with IDA. In some countries we have found it extremely difficult to find subjects with IDA, which led me to comment that the best way to cure IDA is to look for it. We had this problem recently in Thailand and in Morocco, and some other colleagues have reported the same difficulty. There should therefore be a major effort by the WHO to make prevalence data much more accurate so that we can advocate them with a clear conscience. This refers especially to iron prevalence data. I can’t really say much about the prevalence data for vitamin A and iodine, which may be more accurate.

Dr. Mannar: In all of this, what is the influence of zinc and folic acid deficiencies on iron status and vice versa, and is this an important factor, especially during the early years? I wonder whether any work has been done?

Dr. Hurrell: I think that should be left to this afternoon because Dr. Lönnnerdal is going to discuss zinc, and I have already taken one of his interactions. I wouldn’t like to take another one.

Dr. Pettifor: To follow up on the issue that Dr. Zlotkin mentioned, the issue of prevalence. We are talking about micronutrient deficiencies, particularly in the weaning period. If you look at the values, particularly for IDA, the hemoglobin values which have been used vary from 10 to 10.5 to 11 as the cutoff points. What is the recommended cutoff point for IDA in this age group? In the weaning period, it alters prevalence significantly depending on which cutoff point is used.
Dr. Hurrell: I think Dr. Zlotkin can answer that one. He is the pediatrician.

Dr. Zlotkin: The WHO definition is that a hemoglobin under 110 would be defined as anemia in this age group. There is some question about the value or the meaning of this particular value because if anemia is defined based on functional outcomes, it is in my view, and we will have a discussion on this, that the functional impact of anemia is probably not apparent at 110 but it is at some value below that. So for research purposes anemia is defined based on hemoglobin of anywhere between 100 and 110, but the current official recommendation by the WHO is hemoglobin of <110 g/l, less than 11 mg/dl or 110 g/l.

Dr. Tolboom: Going back to Venezuela and then to the Côte d'Ivoire, you said that farmers in Venezuela could have been vitamin A-deficient and that could explain the possible effect of supplementation. What was the vitamin A status of the children in the Côte d'Ivoire? We know from the UNICEF program that there is seasonality in serum retinol levels. Perhaps malaria was already mentioned as an infection that has an influence on serum retinol levels. Could you comment on that?

Dr. Hurrell: The vitamin A status was not measured in the Venezuelan subjects, so we don’t know what the vitamin A status was. It was just a shot in the dark really when we decided to look at vitamin A. In the Côte d'Ivoire all the children had low serum retinol levels, and I think about half of them had serum retinol levels below the cutoff for marginal deficiency, which is 0.7 μmol/l. We also performed this modified relative dose-response test by injecting the children with dehydroretinol and then measuring the retinol/dehydroretinol ratio. Using this methodology, which we did with Dr. Tarnumihardjo who is a specialist in this area, all the children had a low vitamin A status. These children lived in the north of the country, in an area which is now held by opposition rebel forces. The vitamin A intake was very low, and clearly these children were not getting vitamin A supplementation.

Dr. Lozoff: I want to go back to the hemoglobin question. In the literature in the last couple of years some researchers have proposed that the level of 110 is too high for infants and toddlers [3]. It is generally based on Swedish and Honduran studies that Dr. Lönnerdal might comment on. I want to urge anyone who has performed infant studies in which iron supplementation was well supervised, and ideally also included other vitamins, to analyze and publish their results. This would help to determine the level of hemoglobin after supplementation in this age group in various populations. For Costa Rica and Chile, where iron supplementation was very carefully supervised, the average value after supplementation was well above 11. In Costa Rica, of course, it was higher due to the slight elevation, but the mean was 135 g/l. In Chile the mean was above 120 g/l. These observations would not support the movement to reduce the cutoff. It seems as though we need more data before such a change is accepted.

Dr. Lönnerdal: I can respond first to you why we studied the lower cutoff. A colleague of mine did studies in Guatemala, at the same time we were doing studies in Sweden, where breastfeeding is common. When the infants start with weaning foods, they get iron-supplemented complementary foods, meats, and all kinds of iron sources. Their iron intake is quite good, but we found 33% anemia in Swedish infants by 6 months of age. We didn’t quite believe that this was correct. This was similar to what was found in Guatemala, and that is why we wondered if the cutoff at that age is actually correct. Another thing that I would like to add and I will touch upon it from an other angle this afternoon, is that Dr. Abrams and I, together with my Swedish colleagues, did a study in which we looked at iron absorption between 4 and 6 and 6 and 9 months of age [4]. Between 4 and 6 months of age the infant cannot homeostatically control iron absorption. If their iron status is excellent and you give them iron, they will make more and more hemoglobin. We know now from our animal studies that the regulatory machinery for iron absorption is just not there at a young age. They don’t have a developed signaling system. After 6 months of age infants start regulating iron
absorption. In Africa, this is the weaning period and that is another situation, but by using a fairly high cutoff for hemoglobin in the young infant, I think we are fooling ourselves.

Dr. Lozoff: This is a great reminder that even within the infant period, it is important to be very specific about the age periods. In Chile and Costa Rica, all the children were over 12 months of age. So one of the risks is that people are not careful enough about specifying what particular period they are talking about. This is just a warning to all of us.

Dr. Barclay: I would like to address the interaction of calcium and iron. Today we have more and more calcium with calcium-fortified products on the market. In the 1990s there were some short-term absorption studies showing that at high doses calcium decreased iron absorption [5, 6]. What is the current state of knowledge on the longer-term effects of calcium on iron nutrition?

Dr. Hurrell: I think the earlier studies on the effect of higher levels of calcium on iron absorption were single meal studies carried out mainly by Hallberg et al. [6] in Sweden. They showed quite clearly that as the level of calcium increased, iron absorption was reduced. Hallberg et al. [7] did one study on milk formulas with high calcium levels and a milk formula with the same calcium level as human milk, and showed quite a marked difference in iron absorption. From those single meal studies there has been some concern about the influence of calcium on iron absorption. Reddy and Cook [8] then did a multiple meal study in which they looked at the effect of calcium on iron absorption over a 14-day period with a United States-type diet, which contained many different foods. It was a very varied diet, and no effect of calcium was found. Part of the problem in comparing single meal studies with multiple meal studies is that the comparison is always made with the United States diet. People in developing countries do not have a varied diet, but a much simpler monotonous diet. So I am sure that, in a developing country, phytic acid, vitamin C, tea, or calcium could still influence iron absorption. Again the question is can we extrapolate from the United States and Europe to developing countries where the problems really are?

Dr. Gebre-Medhin: I very much enjoyed your presentation; this is evidently the way we should go ahead. Of course it raises a couple of things on which I would like to comment. First is the issue of epidemiology that Dr. Zlotkin has taken up, and I missed the special article by Wolde-Gebriel et al. [9] who did a remarkable study in Ethiopia which showed the prevalence of iron deficiency, vitamin A and iodine, to be at much higher figures than those presented here. I am convinced that if this were done in Nigeria or Egypt or South Africa, they would give more or less the same picture. So we need to do a little more homework on epidemiology. Second is the issue of anemia, iron deficiency and IDA. These three different issues are not always adequately described in the literature. I believe it is very important to always define these three entities. The last comment I have, and a question, is the issue of carrier proteins and their influence on metabolism and infection and protein energy status. In your presentation you did not mention anything about carrier proteins as major determinants and causes of variation. Would you like to comment on that: retinol-binding protein, prealbumin, and the lot?

Dr. Hurrell: I didn’t really look much at carrier proteins in this review. For the interaction of iodine and vitamin A, retinol-binding protein and transthyretin have potential for interaction because retinol-binding protein, which transports vitamin A is almost entirely associated with transthyretin which transports the thyroid hormones. There are fewer studies looking at the vitamin A–iodine interaction, but there are beginning to be more. One other interesting area in relation to vitamin A and iodine is in relation to transcription of thyroid-stimulating hormone. This is blocked by thyroxine and retinoic acid, so retinoic acid also plays a role in regulating thyroid volume. There are some animal studies that found an increased thyroid volume with vitamin A
deficiency, and this is one of the other possible interactions [10]. There are many studies in developing countries indicating other possible interaction, but it is difficult to sift through all of these studies. I only presented those studies which supported interactions of iron, iodine and vitamin A, but I could have looked through and found studies which show no effects. So I gave a general picture of what I believe is the direction of our understanding. But you are right, the binding to carrier proteins could also be a very important variable in these interactions because these proteins are used by many micronutrients.

Dr. Lönnertdal: I would like to come back to the question that Dr. Barclay raised: calcium supplementation and its effect on iron. First it is not easy to really review the literature in detail because the results from these studies are actually in the calcium field and we are looking at the effect on iron. Therefore a year ago we did a meta-analysis which hasn’t been published yet. There have been studies on preterm infants, term infants, young children, school-age children, young women, pregnant women, postmenopausal women, and in all these studies generous levels of calcium were given for 3 months up to 1 year. None of these studies showed an effect on hemoglobin or serum ferritin when they were measured [11]. That is the observational response to the question. With regard to functional response, we have been working on iron transporters, and if a monolayer of human intestinal cells is made in culture to look at the same phenomenon by adding generous levels of calcium, immediately or very soon afterwards in these cells iron absorption and iron transport are impacted. But we have something wonderful in the human body called metabolic adaptation. The intestinal cell will realize that something is happening and take steps to modify this, and therefore up- and downregulation on the iron transport machinery occur soon after the start of calcium supplementation (this has also not been published but will be soon). It will make account of the high calcium and adapt, and therefore there is no long-term effect. Just as Dr. Hurrell said about the single meal studies, many of these are switch-over studies. If suddenly a generous dose of calcium is given, the intestinal cell is going to say ‘what’s happening now?’, and this is when iron absorption is measured, and an effect is seen. But after 2 or 4 weeks the body will deal with this higher level and the intestinal cell is going to be less surprised and take it into account and adapt. I think this explains why very different results are seen when short-term studies are done as opposed to long-term studies.

Mr. Parvanta: Just coming back to the epidemiology issue. I appreciated the comments about defining when we are talking about anemia versus iron deficiency versus IDA, and a lot of people don’t make those distinctions, especially in population-based data. Beyond this problem of not defining what we are talking about, our experience has been that there are a lot of projects that do surveys or assessments of populations, especially just simply doing hemoglobin. First of all a lot of different methods are used and even when the methods are similar, the methodology in training and the level of care that goes into collecting that information is quite variable. For example, right now the heme Q instrument is widely used and we at Centers for Disease Control (CDC) certainly believe in the utility of that instrument and use it quite a bit ourselves. But our experience has shown that because the instrument appears to be so easy to use that not enough care is taken in standardizing procedures and methods. A lot of the time we find differences in results just due to methodology rather than the real situation. I just want to point out that of course the difficulty with iron has been that there has been no agreement on what the indicator of choice is, especially for assessing our population’s iron status or iron deficiency. I am happy to say that we at the CDC have funded the WHO to convene an expert working group or workshop to basically agree on some definitions so that we can perhaps move forward with what we have rather than being in this quandary of what is the indicator to use. A final comment, I feel that a lot of times we talk about the biggest problems in the world being in Africa, Asia and
South America, which is true, but there are other parts of the world. I would especially like to point out that in Central and Eastern Europe, the former Soviet Union, there is a tremendous problem, even in the Middle-East, with regard to iron deficiency, and now there is some evidence even with vitamin A deficiency. At some levels they are subclinical but fairly significant in some surveys we recently have been working on in Jordan for example, and there is some evidence of vitamin A deficiency. Certainly with iron deficiency, I think we just cannot forget that part of the world as another area that requires a lot of interventions.

Dr. Hurrell: I agree.

References
