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THE INFLUENCE OF IRON STATUS ON IODINE UTILIZATION AND THYROID FUNCTION

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■ **Abstract** Despite significant progress, deficiencies of iron and iodine remain major public health problems affecting ≥30% of the global population. These deficiencies often coexist in children. Recent studies have demonstrated that a high prevalence of iron deficiency among children in areas of endemic goiter may reduce the effectiveness of iodized salt programs. These findings argue strongly for improving iron status in areas of overlapping deficiency, not only to combat anemia but also to increase the efficacy of iodine prophylaxis. The dual fortification of salt with iodine and iron may prove to be an effective and sustainable method to accomplish these important goals.

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INTRODUCTION

The risk of multiple, coexisting micronutrient deficiencies is high in developing countries due to monotonous diets based on staple foods of low nutrient density (67, 72). Dietary deficiencies are compounded by increased turnover and/or losses due to endemic infectious diseases, including intestinal parasites and malaria. Infants, children, and pregnant women are particularly vulnerable because of increased needs during growth and pregnancy. Inadequate intake of iodine impairs thyroid function and results in a spectrum of disorders—goiter, cognitive impairment, and congenital abnormalities—collectively referred to as the iodine deficiency disorders (IDDs). Along with iodine, other micronutrient deficiencies, including iron, selenium, and vitamin A, may adversely affect the thyroid. Deficiencies of these micronutrients can act in concert with iodine deficiency to impair thyroid function and modify the response to prophylactic iodine (1, 74, 78).

Despite significant progress, deficiencies of iron and iodine remain major public health problems affecting ≥30% of the global population (66, 68). These deficiencies often coexist in children—in regions of West and North Africa, 20%–38% of schoolchildren may suffer from both goiter and iron deficiency anemia (IDA) (71, 78). This review of the interaction of iodine and iron deficiencies discusses (*a*) the biochemistry and mechanism of the interaction in animal studies, (*b*) human supplementation studies in deficient populations, and (*c*) studies of salt dual fortified with iron and iodine.

ANIMAL STUDIES

Iron Status, Thyroid Function, and Thermoregulation

Initial studies on thyroid hormone metabolism in iron-deficient anemic rats focused on thermoregulation. In comparison with iron-sufficient rats, rats with IDA show decreased plasma triiodothyronine (T3) and thyroxine (T4) concentrations. The normal increase in plasma T3 and T4 concentrations in iron-sufficient rats after cold exposure (4°C) is not found in iron-deficient rats (4, 16, 60). Additionally, in rats with IDA, the increase in thyroid-stimulating hormone (TSH) concentration in response to cold is reduced compared to control animals (60). Thus, although iron-deficient rats are able to increase thyroid hormone production when challenged with cold, their ability to fully up-regulate thyroid hormone metabolism is limited in comparison with control animals (8). Rats made anemic by exchange transfusion also have an impaired ability to up-regulate thyroid metabolism in response to cold, and transfusion to a normal hematocrit (Hct) improves the defect in thyroid up-regulation (5). Infusion of T3 in rats with IDA improves their ability to maintain body temperature at 4°C, whereas T4 infusion had no effect on temperature control (4). These studies suggest (*a*) IDA blunts the TSH response to cold temperature and impairs the conversion of T4 to T3, and (*b*) anemia, rather than tissue iron deficiency, is the critical factor in impaired thyroid response to low temperature (9).

Animals with severe IDA (mean Hct ≈ 16%) have a reduced TSH response to lower circulating T3 and T4 concentrations (6), whereas no effect was found in mild IDA (mean Hct ≈ 31%) (60). T3 turnover and elimination is significantly lower in iron-deficient animals than in iron-sufficient controls (6). At 15°C ambient temperature, T4 and T3 disposal rates are lower in iron-deficient rats than in iron-sufficient controls (lower by 48% and 28%, respectively) (8). Nuclear [^{125}I]T3 binding may also be reduced by iron deficiency (56).

Peripheral metabolism of thyroid hormone is also affected by IDA. Anemic rats have decreased hepatic 5′-deiodinase activity, an enzyme that catalyzes the conversion (and activation) of T4 to T3 (6, 10, 55). The hepatic deiodinase is a selenocysteine-containing protein, and selenium deficiency reduces its activity and may impair thyroid metabolism in iodine-deficient populations (74). The impairment of 5′-deiodinase activity is greater in severe IDA than in mild IDA (activity lower by 75% and 25%, respectively) (10). In IDA, not only is less T4 converted to T3, but conversion to reverse T3, a physiologically inactive metabolite, also is increased. Although reduced hepatic 5′-deiodinase activity in IDA may be at least partly due to lower plasma T4 concentrations, normalizing plasma T4 concentrations in iron-deficient animals did not normalize hepatic 5′-deiodinase activity (10). This suggests 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.

Mechanisms of the Impairment of Thyroid Function in Iron Deficiency

Until recently, the mechanism by which iron deficiency impairs thyroid metabolism was unclear. IDA may induce alterations in central nervous system control of the thyroid axis (8) and reduce T3 binding to hepatic nuclear receptors (57). Although impaired peripheral metabolism of thyroid hormone may also play a role, Beard et al. (8) argued the effect of IDA on hepatic 5′-deiodinase is minimal. Earlier in vitro studies reported outer ring deiodinase activity was not affected by either ferric or ferrous iron (37). IDA may also impair thyroid metabolism by decreasing oxygen transport, similar to the thyroid impairment in hypoxia (26, 59). Chronically hypoxic children have lower levels of circulating T4 and T3 and increased concentrations of reverse T3 (47). In contrast, acute exposure to hypoxic stress in healthy adults rapidly elevates plasma T4 and T3 concentrations, which are maintained during the entire period of exposure (3, 51). In thyroidectomized rats, iron absorption was decreased in comparison with intact controls, and thyroid hormone replacement increased absorption in the thyroidectomized group (17).

Finally, the association between hypothyroidism and anemia may be physiologic to some extent. Hypothyroidism reduces need for oxygen transport and delivery to peripheral tissues (43). Also, negative energy balance reduces circulating thyroid hormone concentrations in fasting rats (36, 40, 52), and anorexia and decreased food intake is characteristic of IDA.

As discussed below, a characteristic effect of IDA in goitrous children is a blunting of the reduction in thyroid volume in response to iodine repletion. This may at

least partially be explained by the interaction of nitric oxide with hemoglobin (Hb). Nitric oxide is a potent vasodilator produced in endothelial cells (39). Binding of nitric oxide to hemes and thiols of Hb varies as a function of HbO_2 saturation (45). Moreover, erythrocyte/thiol-mediated vasodilator activity is inversely proportional to HbO_2 saturation (45). This inverse relationship may lead to vasodilation in the highly vascular thyroid and increase thyroid volume in IDA. However, it remains unclear if Hb actually delivers nitric oxide bioactivity (31, 39).

Recent studies suggest the mechanism for impaired thyroid hormone metabolism in IDA is reduced activity of the iron-dependent enzyme, thyroid peroxidase (TPO). TPO is a glycosylated heme enzyme active at the apical membrane of the thyrocyte (61). It catalyzes the two initial steps of thyroid hormone synthesis—iodination of thyroglobulin and coupling of the iodotyrosine residues (Figure 1) (18). Although these events occur at the apical membrane, most TPO in the thyrocyte is found in the endoplasmic reticulum and the perinuclear membrane (21, 38, 49). Only ≈30% of synthesized TPO translocates to the apical cell surface (23, 38), and heme insertion into TPO is necessary for this translocation (24). Treatment with hemin, a chemical derivative of Hb, increases the quantity and activity of TPO at the apical cell surface level by 20% and 120%, respectively (24) (Figure 2). Conversely, treatment with succinyl acetone, a specific inhibitor of heme synthesis, decreases the quantity and activity of TPO at the cell surface by 25%–37% and 68%–92%, respectively (24) (Figure 3). As in earlier studies (22, 27), these data suggest a portion of the TPO at the apical surface is inactive because it is not bound to heme. Insertion of heme into lactoperoxidase, an enzyme that shares similarities with TPO, does not require modification of heme before incorporation into the enzyme (15).

A recent study examined whether IDA reduces TPO activity. Weanling Sprague-Dawley rats were assigned to seven groups (30). Three groups (ID-3, ID-7, and ID-11) were fed iron-deficient diets containing 3, 7, and 11 μg iron/g. An iron-sufficient diet was given to three pair-fed groups and given ad libitum to a control group. After four weeks, Hb and circulating T3 and T4 concentrations were significantly lower in the iron-deficient groups than in the control group ($p < 0.001$) (Table 1). TPO activity (by both guaiacol and iodide assays) was markedly reduced by iron deficiency ($p < 0.05$). Compared with the control animals, 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 ($p < 0.05$) (Figure 4). These data suggest impaired thyroid function in IDA is due to reduced TPO activity, likely caused by decreased intracellular heme concentrations (30).

HUMAN STUDIES

Studies in Anemic Women in Industrialized Countries

Lukaski et al. (41) found no significant differences in thyroid hormone and TSH concentrations between iron-deficient and iron-sufficient women at room

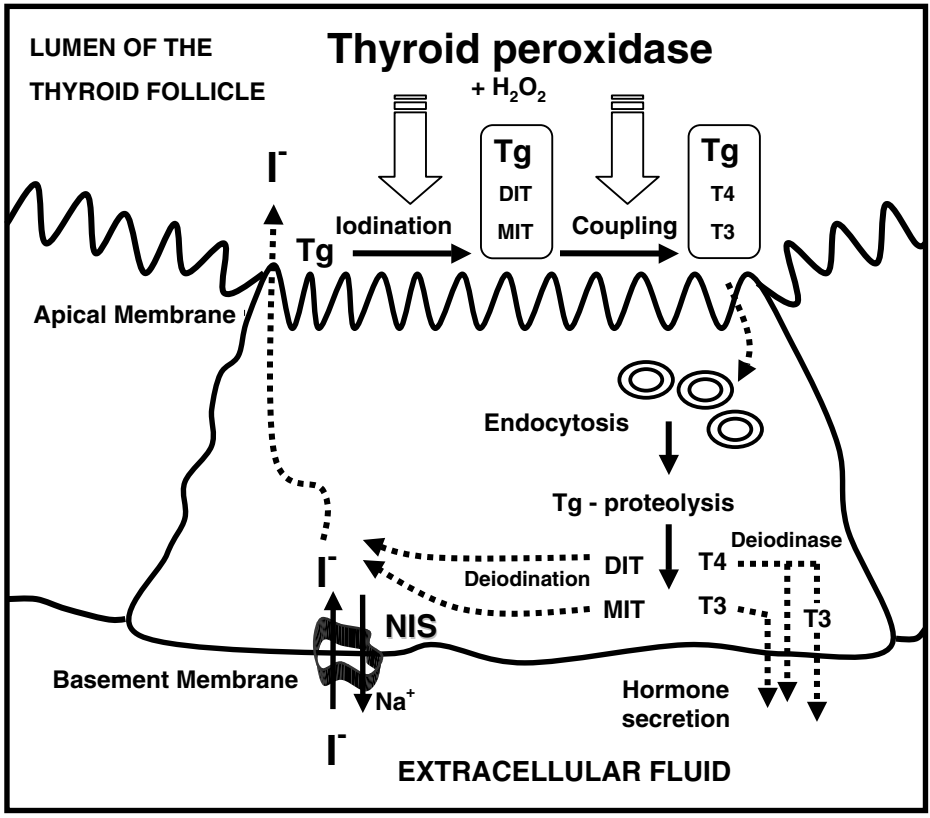

Figure 1 The role of thyroid peroxidase in the iodine pathway in the thyroid cell. Iodide (I^-) is transported into the thyrocyte by the sodium iodide symporter (NIS) at the basal membrane and migrates to the apical membrane. The I^- is oxidized by thyroid peroxidase (TPO) together with hydrogen peroxidase (H_2O_2) and attached to tyrosyl residues in thyroglobulin (Tg) to produce the hormone precursors iodotyrosine (MIT) and diiodotyrosine (DIT). In a second step catalyzed by TPO, the residues then couple to form thyroxine (T4) and triiodothyronine (T3) within the Tg molecule in the follicular lumen. Tg enters the cell by endocytosis and is digested. T4 and T3 are released into the circulation, and nonhormonal iodine on MIT and DIT is recycled within the thyrocyte.

temperature. However, in response to cold exposure, increases in TSH, T4, and T3 were reduced 5%–7% in iron-deficient women compared with controls. Martinez-Torres et al. (44) reported a nonsignificant 10% decrease in T3 concentrations in adults with moderate-to-severe IDA (mean Hb 75 g/L) compared with iron-sufficient controls. Beard et al. (7) found similar TSH concentrations, but significantly lower T3 and T4 concentrations (reduced by 26% and 22%, respectively) in anemic women (mean Hb 110 g/L) compared with healthy controls. Iron

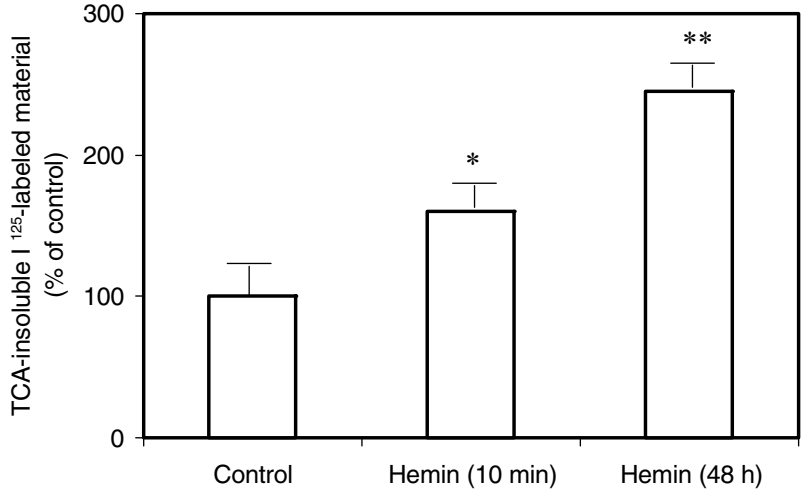

Figure 2 Effect of hemin on cell surface thyroid peroxidase (TPO) activity in CHO cells. Cells were incubated with or without hemin (20 μM) before assaying TPO activity. Statistically significant differences compared with control were $^{*}p < 0.05$; $^{**}p < 0.001$. TCA, trichloroacetic acid. Adapted from Reference 24.

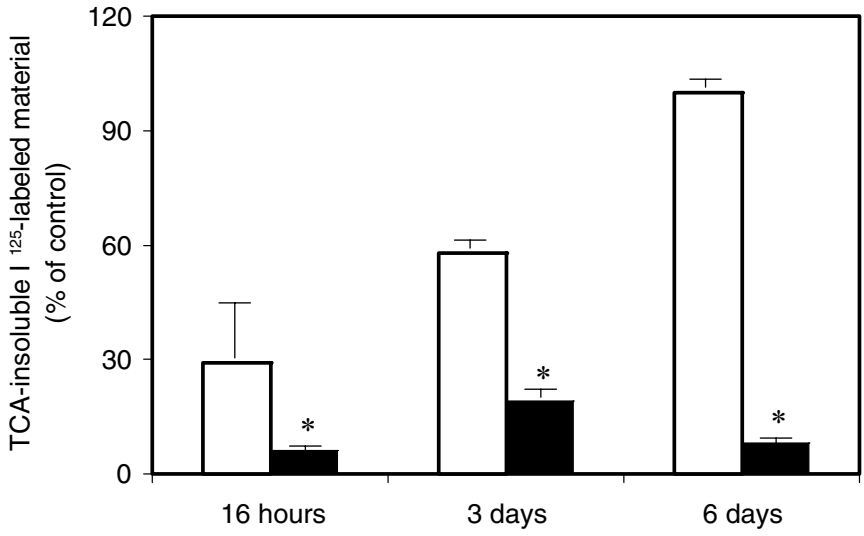

Figure 3 Effect of succinyl acetone (SA) (an inhibitor of heme synthesis) on the activity of thyroid peroxidase at the surface of CHO cells, after incubation for 16 hours, 3 days, or 6 days with (*dark bars*) or without (*light bars*) 250 μM SA. Activity was measured and expressed as a percentage of control at 6 days. Statistically significant differences compared with control were $^{*}p < 0.05$. TCA, trichloroacetic acid. Adapted from Reference 24.

TABLE 1 Hemoglobin and plasma total thyroxine (T4) and total triiodothyronine (T3) concentrations in weanling rats fed iron-deficient diets containing 3, 7, and 11 μg Fe/g for 29 days (ID-3, ID-7, ID-11), their pair-fed controls (PF-3, PF-7, PF-11), and control rats that consumed the iron-sufficient diet ad libitum (CN). Data from Reference 30

Group	N	Hemoglobin (g/L)	T3 (ng/L)	T4 (μg/L)
ID-3	12	40.3 ± 5.2^{d}	32.4 ± 9.3^{b}	2.1 ± 0.5^{c}
PF-3	11	146.2 ± 11.6^{a}	42.3 ± 3.7^{ab}	2.6 ± 0.6^{bc}
ID-7	12	58.4 ± 5.9^{c}	33.5 ± 5.5^{b}	2.4 ± 0.3^{bc}
PF-7	12	137.9 ± 6.7^{a}	47.6 ± 6.0^{a}	2.9 ± 0.5^{ab}
ID-11	12	72.4 ± 6.1^{b}	31.2 ± 5.4^{b}	2.7 ± 0.5^{b}
PF-11	12	135.4 ± 5.1^{a}	51.1 ± 13.9^{a}	2.9 ± 0.9^{ab}
CN	12	136.3 ± 10.9^{a}	48.5 ± 11.4^{a}	3.9 ± 1.1^{a}

Results are means ± SD. Means in a column without a common letter differ; $P < 0.05$.

supplementation of the anemic women increased mean Hb by 17 g/L and partially normalized thyroid hormone concentrations (7).

Hypothyroidism and Anemia

Although several studies have found a high prevalence of anemia (25%–50%) in hypothyroid patients (14, 32), anemia was only rarely due to iron deficiency. Serum ferritin concentrations and total iron-binding capacity may be lower in hypothyroid adults compared with euthyroid controls (19). In hypothyroid patients with low hemoglobin and serum iron levels, Hb concentrations increase with T4 replacement, but the Hb increase is greater when T4 is given with iron (32). Poor iron absorption in hypothyroidism may be due to achlorhydria (43, 53).

Cross-Sectional Studies in Developing Countries

Cross-sectional studies in developing countries looking for associations between IDD and IDA have produced equivocal results. In Ethiopian children, there was no correlation between iron status and goiter rate or thyroid hormone concentrations (65). There was no significant difference in the prevalence of anemia comparing goitrous and nongoitrous subjects in the Philippines (25). However, in a national screening of schoolchildren in Iran ($n = 2917$), there was 3.8-fold higher risk of goiter in children with low serum ferritin concentrations (2). In a second study in Ethiopian children, circulating T3 concentrations were correlated with serum iron and transferrin saturation (64). In an area of mild iodine deficiency in Turkey, thyroid hormone levels of children with anemia were not significantly different from those without anemia, and there was no significant correlation between thyroid hormones and iron status (69). In schoolchildren in Côte d'Ivoire, the relative

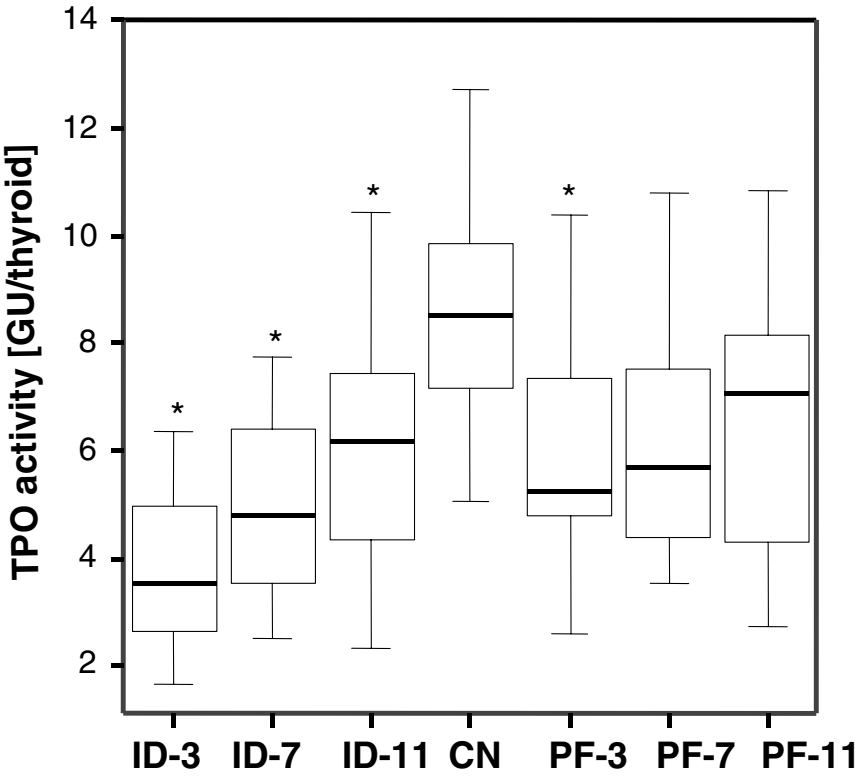

Figure 4 Thyroid peroxidase (TPO) activity expressed in guaiacol units (GU) per thyroid in Fe-deficient rats (ID-3, ID-7, ID-11), their pair-fed controls (PF-3, PF-7, PF-11), and control rats that consumed food ad libitum (CN). The plots show the median, 75th, and 25th percentiles as boxes, and the ranges as whiskers, n = 11–12. The iron-deficient diets contained 3, 7, and 11 μg iron/g. Statistically significant differences compared with CN were $^{*}p < 0.05$. Adapted from Reference 30.

risk of goiter was 1.9 (95% CI: 1.5, 2.3) in children with IDA compared with iron-sufficient children (71).

Impaired Efficacy of Iodized Oil in Anemic Children

A series of recent intervention studies in West African children have investigated whether goitrous children with IDA have a normal response to oral iodine supplementation (71) and whether iron supplementation in goitrous children with IDA improves their response to oral iodized oil (70) and iodized salt (29). The studies were done in an area of endemic goiter in western Côte d'Ivoire. In 1997, the median urinary iodine concentration (UIC) and the goiter rate by palpation in school-age children in this region were 28 μg/L and 45%, respectively (71),

indicating moderate-to-severe IDD (68). Côte d'Ivoire began universal salt iodization in 1997, and by late 1998, iodized salt was introduced into the western region. By late 1999, >80% of households were using iodized salt at a household level of 20–30 ppm. The first studies (70, 71) were done in 1997–98, before the introduction of iodized salt, whereas the final study (29) was done in 2000, 12–18 months after the introduction of iodized salt.

In the first study (71), iodine and iron status was measured in schoolchildren (n = 419). Thyroid gland volume (Tvol) was measured ultrasonographically (73) and TSH, T4, and UIC were determined. Screening for IDA was done using Hb, whole-blood zinc protoporphyrin (ZnPP), serum ferritin (SF), and serum transferrin receptor (TfR). All goitrous 6- to 12-year-old children were invited to join an intervention study and divided into two groups: Group 1 consisted of goitrous children without anemia, and group 2 consisted of goitrous children with IDA. IDA was defined as Hb < 110 g/L + SF < 12μg/L or Hb < 11 g/dl + TfR >8.5 mg/L + ZPP > 40 μmol/mole heme (13, 75). Throughout the study, the investigators were blind to the group assignment of the children. Each child in groups 1 and 2 received an oral dose of 0.4 ml iodized poppy seed oil (Lipiodol®, Guerbet, France) containing 200 mg of iodine and was followed for 30 weeks.

At baseline, median UI was 27–29 μg/L, indicating moderate-severe IDD (65). Mean (±SD) Hb in group 1 was 125 ± 4 g/L, whereas mean (±SD) Hb in group 2 was 97 ± 8 g/L, with 20% of the children having an Hb < 90 g/L. Of the 109 children who began the study, 104 completed it. The 200 mg oral dose of iodine maintained median UI above the cutoff value (100 μg/L) for risk of iodine deficiency (68) in both groups over the 30 weeks of follow-up. Table 2 shows the changes in Tvol in groups 1 and 2 over the course of the study. At 15 and 30 weeks, Tvol was significantly reduced in group 1 compared with group 2 ($p < 0.001$). At 30 weeks, the mean percentage change in Tvol from baseline was –45% in group 1 and –22% in group 2. A sharp difference in goiter prevalence was apparent at 15 and 30 weeks, when goiter rates were 62% and 64% in group 2 but only 31% and 12% in group 1 (Figure 5). Table 3 shows the changes in TSH and T4 over the 30 weeks of follow-up. In group 2 at 1 week, there was no change in mean serum T4 but a significant transient rise in the median TSH value, consistent with a mild Wolff-Chaikoff effect. Median TSH values at 15, 30, and 50 weeks were reduced significantly ($p < 0.01$) compared with baseline in group 1. At 15 and 30 weeks, median TSH values were significantly lower in group 1 compared with group 2 ($p < 0.01$). Mean serum T4 increased significantly from baseline in group 1 at 30 weeks ($p < 0.01$), and at 15 and 30 weeks, T4 values in group 1 were significantly greater than in group 2 ($p < 0.001$). In this study, both anatomic (thyroid size) and biochemical (TSH, T4) measures of thyroid function were significantly improved by iodized oil in the nonanemic children compared with the children with IDA.

Iron Supplementation Improves Efficacy of Iodized Oil

Beginning at 30 weeks after administration of oral iodine, each child in group 2 received 60 mg oral iron as ferrous sulfate four days per week for 12 weeks (70).

TABLE 2 Thyroid volume in goitrous children without anemia (group 1) (n = 53) and with iron-deficient anemia (group 2) (n = 51) 10, 15, 30, 52, and 65 weeks after receipt of 200 mg oral iodine. Group 2 received 60 mg oral iron as ferrous sulfate 4 times/week from week 30 to week 42. Data from References 70 and 71

	Group 1	Group 2
Thyroid volume (ml) at baseline	8.5 ± 2.0	8.1 ± 1.9
Groups 1 and 2 received 200 mg of oral iodine		
Thyroid volume (ml) at 10 weeks	6.5 ± 1.7[1]	6.5 ± 2.6[1]
Change (%) from baseline	−22.3 ± 17.3	−20.0 ± 19.5
Thyroid volume (ml) at 15 weeks	5.1 ± 1.5[1,3]	6.3 ± 2.4[1]
Change (%) from baseline	−30.7 ± 14.8	−22.8 ± 18.8
Thyroid volume (ml) at 30 weeks	4.6 ± 1.5[1,3]	6.3 ± 2.1[1]
Change (%) from baseline	−45.5 ± 12.0	−21.8 ± 17.2
Group 2 received 60 mg oral iron as ferrous sulfate 4 times/week		
Thyroid volume (ml) at 50 weeks	4.3 ± 1.3[1,3]	5.4 ± 1.7[1]
Change (%) from baseline	−46.9 ± 13.7	−34.8 ± 14.2
Thyroid volume (ml) at 65 weeks	**4.5 ± 1.5[1,2]	5.0 ± 1.5[1]
Change (%) from baseline	−46.1 ± 12.9	−38.4 ± 13.6

Values are means ± SD.To reduce the effects of variability among individuals, the percentage change from baseline was calculated for each child before the means were derived.

[1] $p < 0.001$ versus baseline.

[2] $p < 0.05$ between groups.

[3] $p < 0.001$ between groups.

Measurements of iron and iodine status (described above) were repeated at 50 weeks and at 65 weeks (8 and 23 weeks after completion of iron supplementation). Iron supplementation in group 2 resulted in an increase in mean Hb (SD) from 97(8) g/L at 30 weeks to 122(8) g/L at 50 weeks. Only 6 of the 51 children in group 2 remained anemic at 50 weeks. Change in Tvol from baseline in group 2, which had plateaued at weeks 10 through 30, began to fall again after iron supplementation, to a mean (SD) of –34.8 (14.2) and –38.4 (13.6) at 50 and 65 weeks, respectively (Table 2). Goiter prevalence in group 1, which had remained at 62%–64% from weeks 10 through 30, was reduced after iron supplementation to 31% and 20% at 50 and 65 weeks (Figure 5). These findings are supported by a recent randomized, controlled trial in iodine-sufficient adolescent Iranian girls with iron deficiency, where iron and iron-plus-iodized oil supplementation produced significant improvements in thyroid hormone levels compared with iodine alone or placebo (20).

Iron Supplementation Improves Efficacy of Iodized Salt

The final study (29) was a controlled trial of iron supplementation in goitrous children with iron deficiency who were receiving iodized salt. Schoolchildren (n = 1014) were screened for iron and iodine status. Spot urine samples were collected

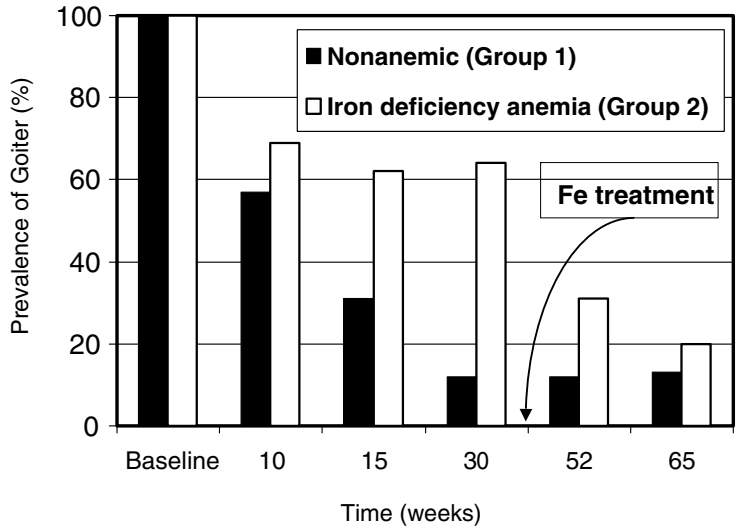

Figure 5 Percentage of children in group 1 (nonanemic) (n = 53) and group 2 (iron-deficient anemic) (n = 56) with goiter 10, 15, 30, 52, and 65 weeks after oral administration of 200 mg I, as assessed by ultrasound. Group 2 received 60 mg oral iron as ferrous sulfate 4 times/week from week 30 to week 42. Adapted from References 70 and 71.

for measurement of UIC. Tvol was measured by ultrasound, and normative values in children age 6–12 years were used to define goiter (73). Blood was collected by venipuncture for determination of TSH, T4, Hb, ZnPP, SF, and TfR. Random salt samples (n = 213) from households of children in the screening were collected for determination of iodine concentration. From the screening, all goitrous children with iron deficiency were invited to join a double-blind intervention study. Of the children enrolled (n = 169), 85% were anemic (Hb < 110 g/L) and 15% were iron deficient but not anemic. They were randomized to two groups: One group received 60 mg oral iron as ferrous sulfate four days per week for 16 weeks; the second group received placebo. All children received a single 400 mg oral dose of albendazole (Zentel®, SmithKline Beecham) at baseline. At 6, 12, and 20 weeks, measurements of iron and iodine status were repeated.

In the screening, the median (range) UIC was 162 (16–1017) μg/L. Only 1% and 3% of the children had a UI < 20 μg/L and <50 μg/L, respectively. Mean (±SD) salt iodine content was 25 ± 18 μg/g. Despite optimal UIC and salt iodine levels, the prevalence of goiter by ultrasound was 59%. Median TSH and mean T4 concentrations were within the normal reference range. The prevalence of iron deficiency was 38%, and 23% of children were both goitrous and iron deficient.

Of the 169 children who began the study, 166 completed it. Over 20 weeks, mean (±SD) Hb improved from 110 ± 10 to 124 ± 9 in the iron group ($p < 0.05$) but did not change significantly in the placebo group. At 20 weeks, the prevalence

TABLE 3 Changes in whole blood thyrotropin (TSH), serum total thyroxine (T4), and urinary iodine concentration (UIC) in goitrous children with anemia (group 2) and without anemia (group 1) 10, 15, 30, 52, and 65 weeks after receipt of 200 mg oral iodine. Group 2 received 60 mg oral iron as ferrous sulfate 4 times/week from week 30 to week 42. Data from References 70 and 71

	TSH (mU/L)		T4 (nmol/L)		UIC (μg/L)	
Weeks	**Group 1**	**Group 2**	**Group 1**	**Group 2**	**Group 1**	**Group 2**
0	1.1 (1.1–1.4)	0.8 (0.8–1.4)	110 ± 22	130 ± 28[3]	29 (30–47)	27 (28–46)
1	1.1 (1.1–1.5)	2.1[1,4] (2.0–2.5)	113 ± 22	131 ± 27[3]	992[2] (919–1500)	1210[2,3] (1450–2490)
5	0.6[2] (0.5–0.7)	0.7 (0.7–1.0)	115 ± 21	100 ± 22	281[2] (262–358)	359[2] (331–445)
10	0.6[2] (0.5–0.8)	0.8 (0.7–1.0)	110 ± 26	101 ± 25[1]	168[2] (165–231)	176[2] (172–266)
15	0.5[2] (0.4–0.6)	0.8[3] (0.8–1.0)	122 ± 24	96 ± 17[1,4]	181[2] (165–218)	176[2] (172–266)
30	0.6[2] (0.5–0.6)	1.0[4] (1.1–1.4)	156 ± 30[1]	123 ± 30[4]	125[2] (115–143)	143[2] (128–180)
50	0.7[1] (0.6–0.9)	0.9 (0.8–1.2)	134 ± 31	131 ± 28	94[2] (87–115)	97[2] (85–119)
65	0.8 (0.7–1.2)	0.8 (0.7–1.3)	125 ± 27	119 ± 23	62[1] (46–89)	59[1] (43–87)

Values are medians (95% CI) or means ± SD.

[1] $p < 0.01$ versus baseline.

[2] $p < 0.001$ versus baseline.

[3] $p < 0.01$ between groups.

[4] $p < 0.001$ between groups.

of anemia and iron deficiency was 33% and 39% in the Fe group, and 63% and 52% in the placebo group. Table 4 shows the changes in Tvol and goiter prevalence in the iron and placebo groups. At 12 and 20 weeks, Tvol was significantly reduced in the iron group compared with the placebo group. At 20 weeks, the mean (±SD) percentage change in Tvol in the iron and placebo groups was –22.8 ± 10.7% and –12.7 ± 10.1%, respectively ($p < 0.01$ between groups). At 20 weeks, the goiter rate was significantly lower ($p < 0.02$) in the iron group compared with the placebo group. Median TSH and mean serum T4 concentrations remained within the normal range in both groups throughout the study and there were no significant differences in these measures between groups or compared with baseline at 6, 12, and 20 weeks (Table 5). Median UIC throughout the study was above the 100 μg/L cutoff value for risk of iodine deficiency (68).

In these studies in West Africa, the iron status of goitrous children modified their response to iodine prophylaxis. In both studies, iodine was less efficacious in children with greater anemia at baseline and/or in those with a poorer response to iron treatment. In the first study (71), multiple regression of percentage change

TABLE 4 Changes in thyroid volume and goiter prevalence in the children in the iron-treated (n = 85) and placebo groups (n = 81) after 6, 12, and 20 weeks. Data from Reference 29

Thyroid volume	Iron treated (n = 85)	Placebo (n = 81)
Baseline (mL)	5.6 (3.5 – 16.4)	5.8 (3.4 – 24.7)
6 weeks (mL)	5.6 (2.9 – 15.4)	5.8 (2.9 – 22.5)
% change from baseline	−0.9 ± 13.4	3.4 ± 13.5
Number subjects with goiter	58 [68]	64 [78]
12 weeks (mL)	4.9 (2.5 – 16.0)[1]	5.2 (2.4 – 22.7)
% change from baseline	−13.2 ± 11.6	−7.9 ± 11.1
Number subjects with goiter	46 [54]	51 [63]
20 weeks (mL)	4.3 (2.1 – 12.9)[2,3]	5.1 (2.1 – 21.4)[1]
% change from baseline	−22.8 ± 10.7[4]	−12.7 ± 10.1
Number subjects with goiter	37 [43][4]	50 [62]

As means ± SD, medians (range), or number [%]. To reduce the effects of variability among individuals, % change from baseline was calculated for each child before deriving means.

[1,2]Significantly different from baseline: [1]$p < 0.05$; [2]$p < 0.01$.

[3,4]Significantly different from placebo: [3]$p < 0.05$; [4]$p < 0.01$.

TABLE 5 Changes in whole blood thyrotropin, serum thyroxine, and urinary iodine in the children in the iron-treated (n = 85) and placebo groups (n = 81) after 1, 6, 12, and 20 weeks. Data from Reference 29

	Thyrotropin (mU/L)		Thyroxine (nmol/L)		Urinary iodine (μg/L)	
Time	**Iron**	**Placebo**	**Iron**	**Placebo**	**Iron**	**Placebo**
0	0.5 (0.3–6.0)	0.5 (0.2–2.0)	109 ± 30	121 ± 39	155 (35–449)	151 (22–652)
1 week	0.6 (0.2–3.8)	0.6 (0.3–2.4)	99 ± 29	105 ± 25	178 (15–1013)	140 (33–676)
6 weeks	0.6 (0.3–2.0)	0.6 (0.2–1.9)	102 ± 24	106 ± 30	176 (33–1129)	179 (26–898)
12 weeks	0.7 (0.1–2.3)	0.7 (0.2–2.4)	121 ± 25	120 ± 32	128 (13–505)	135 (25–373)
20 weeks	0.7 (0.7–4.2)	0.8 (0.2–4.2)	105 ± 25	104 ± 29	110 (17–271)	125 (23–445)

As means ± SD or medians (range).

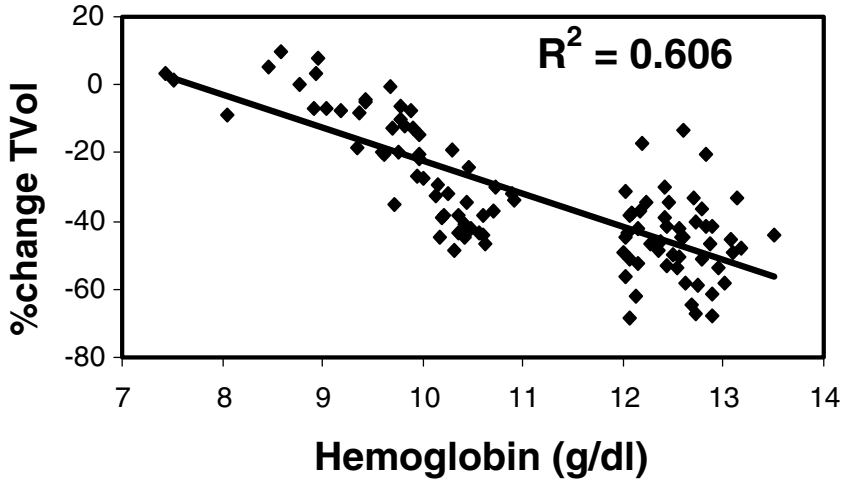

Figure 6 Correlation between baseline hemoglobin (Hb) and percentage change in thyroid volume from baseline to 30 weeks in children in group 1 (Hb concentration >12 g/dl) and group 2 (Hb concentration < 11 g/dl). Adapted from Reference 71.

in Tvol at 30 weeks on Hb and serum retinol and selenium concentrations was done. The regression of percentage change in Tvol on Hb was highly significant ($p < 0.001$), but adding serum retinol or serum selenium did not improve the prediction. There was a strong correlation ($r^2 = 0.606$) between Hb and percentage change in Tvol (Figure 6). Similarly, in the final study, baseline Hb negatively correlated with percentage change in Tvol in both the iron and placebo groups, whereas improvement in Hb from baseline to 20 weeks was positively associated with percentage change in Tvol (29).

DUAL FORTIFICATION OF SALT WITH IODINE AND IRON

Dual Fortification of Salt with Potassium Iodide and Encapsulated Ferrous Sulfate

Because IDA in children reduces the efficacy of iodine prophylaxis (29, 70, 71), the cofortification of iodized salt with iron could be beneficial, not only to combat anemia, but also to improve the efficacy of iodine in salt in populations with a high prevalence of IDA. Salt is a good fortification vehicle, particularly in rural Africa and Indonesia, because in poor regions of subsistence farming, salt is one of few regularly purchased food items (28, 46, 58). In the mountains of northern Morocco, the goiter rate among schoolchildren is 53%–64%, and 25%–35% suffer from IDA (11, 72, 76). Based on data from three-day weighed food records, local salt consumption is 5–12 g/day (77). Thus, the dual fortification of salt with iodine and iron could be a sustainable method to prevent both iodine and iron deficiencies.

However, ensuring the stability and bioavailability of iron and iodine in dual-fortified salt is difficult (42, 50, 54). In the presence of ferrous ions and oxygen, the iodate or iodide moiety of the dual-fortified salt is unstable due to oxidation of iodine to I_2 and subsequent loss of I_2 (62). Ferrous iron is readily oxidized to the generally less bioavailable ferric form (33), and both ferric and ferrous iron can combine with impurities in the salt to give unacceptable yellow to brown off-colors (62). Placing a physical barrier around the iron could prevent these adverse interactions. The benefits of encapsulation of ferrous iron have been shown in studies in Kenya, where the iodine content of salt dual fortified with iodine and microencapsulated ferrous fumarate was generally stable during salt distribution and retail (48).

Based on this idea, a dual-fortified salt was developed with iodine (25 μg iodine/g as potassium iodide) and iron (1 mg iron/g as ferrous sulfate encapsulated with partially hydrogenated vegetable oil). In a nine-month, double-blind intervention trial, 6- to 15-year-old children (n = 377) were randomized at the household level to receive either iodized salt (IS) or dual-fortified salt (DFS) (79). At baseline, UIC and Tvol were measured, and blood was collected by venipuncture for determination of TSH, T4, Hb, SF, ZnPP, and TfR. Each household was provided 2 kg of fortified salt at the beginning of each month for 40 weeks. At 10, 20, and 40 weeks, all baseline measurements were redone.

In the DFS group, hemoglobin and iron status improved significantly compared with the IS group ($p < 0.05$). The prevalence of Fe-deficiency anemia was reduced from 35% to 8% in the DFS group ($p < 0.001$). Table 6 shows the change in Tvol in the two groups. At 40 weeks, mean Tvol in the DFS group was significantly decreased compared with baseline ($p < 0.001$) and compared with the IS group

TABLE 6 Thyroid volume and change in thyroid volume from baseline in children receiving iodized salt (n = 184) or dual-fortified salt containing iodine and encapsulated ferrous sulfate (n = 183) after 10, 20, and 40 weeks. Data from Reference 79

Thyroid volume	Iodized salt	Dual-fortified salt
Baseline (mL)	8.9 ± 3.4	9.1 ± 3.7
10 weeks (mL)	8.7 ± 3.9	9.1 ± 2.8
Percentage change from baseline	−2.9 ± 12.4	−1.4 ± 11.9
20 weeks (mL)	8.3 ± 2.7	7.5 ± 3.4[3]
Percentage change from baseline	−6.2 ± 11.6	−16.9 ± 11.1[4,6]
40 weeks (mL)	7.3 ± 2.4[1]	5.7 ± 2.1[5,7]
Percentage change from baseline	−18.0 ± 6.6[2]	−37.8 ± 9.1[5,8]

Values are means ± SD.

[1,2]Significantly different from baseline of iodized salt group: [1]$p < 0.02$; [2]$p < 0.05$.

[3,4,5]Significantly different from baseline of dual-fortified salt group: [3]$p < 0.02$; [4]$p < 0.05$; [5]$p < 0.001$.

[6]Significantly different from iodized salt group at 20 weeks: $p < 0.05$.

[7,8]Significantly different from iodized salt group at 40 weeks: [7]$p < 0.05$; [8]$p < 0.01$.

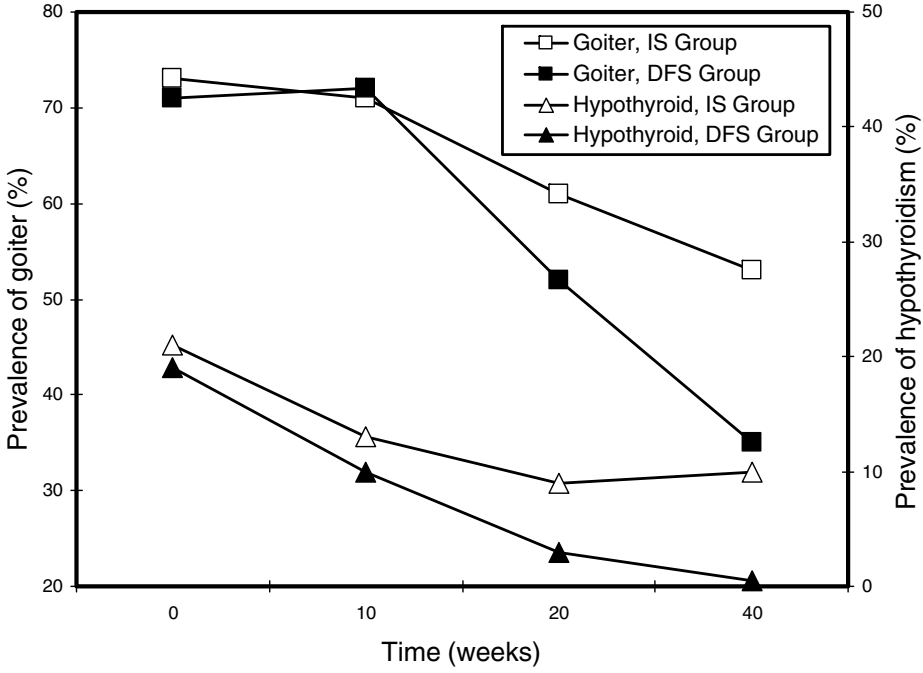

Figure 7 The probability of goiter and hypothyroidism was significantly reduced in children receiving dual-fortified salt containing iodine and encapsulated ferrous sulfate (DFS) (n = 183) compared with those receiving iodized salt (IS) (n = 184) over 40 weeks ($p < 0.01$). Adapted from Reference 79.

($p < 0.05$). At 40 weeks, the mean (±SD) percentage change in Tvol from baseline in the DFS and IS groups was –37.8 ± 9.1% and –18.0 ± 6.6%, respectively ($p < 0.01$). At 40 weeks, the goiter rate was significantly decreased in the DFS group compared with the IS group ($p < 0.001$). As modeled by logistic regression, the probability of goiter was significantly reduced in the DFS group compared with the IS group, and the group difference increased with time ($p < 0.01$ in a comparison of time-and-group model relative to time-only model) (Figure 7) (74).

Table 7 shows the changes in UIC, TSH, and T4 in the two groups. There were no significant differences in median UIC between the two groups throughout the study. At 20 and 40 weeks, median UIC was well above the 100 μg/L cutoff value for risk of iodine deficiency (68). There was a nonsignificant decrease in median TSH in both groups over the course of the study; median TSH was within the normal range in both groups throughout the study. Mean serum T4 increased significantly from baseline in the DFS group ($p < 0.02$) and was significantly greater than in the IS group at 20 and 40 weeks ($p < 0.05$). At 20 and 40 weeks, the prevalence of hypothyroidism (T4 < 65 nmol/L) was significantly reduced in the DFS group compared with the IS group ($p < 0.001$).

TABLE 7 Concentrations of serum total thyroxine (T4), whole-blood thyrotropin (TSH), and urinary iodine (UIC) in children receiving iodized salt (IS) (n = 184) or dual-fortified salt containing iodine and encapsulated ferrous sulfate (DFS) (n = 183) after 10, 20, and 40 weeks. Data from Reference 79

	T4 (nmol/L)		TSH (mU/L)		UIC (μg/L)	
Time	**IS**	**DFS**	**IS**	**DFS**	**IS**	**DFS**
Baseline	82.1 ± 17.3	82.8 ± 19.8	0.9 (0.4–6.2)	0.9 (0.4–27.0)	18 (0–127)	16 (0–143)
10 weeks	91.4 ± 23.8	96.6 ± 24.3	1.0 (0.3–2.9)	0.9 (0.3–3.2)	79[4] (12–488)	87[5] (19–511)
20 weeks	89.8 ± 19.9	103.5 ± 20.2[1,2]	1.2 (0.4–14.9)	1.1 (0.3–8.6)	179[4] (22–432)	183[5] (31–529)
40 weeks	85.3 ± 12.7	102.2 ± 17.4[1,3]	0.6 (0.3–1.9)	0.7 (0.2–2.4)	182[4] (14–474)	189[5] (23–406)

Values are means ± SD or medians (range).

[1,4]Significantly different from baseline of DFS group: [1]$p < 0.02$; [4]$p < 0.001$. [2]Significantly different from IS group at 20 weeks: $p < 0.05$.

[3]Significantly different from IS group at 40 weeks: $p < 0.05$. [5]Significantly different from baseline of IS group: $p < 0.001$.

A multiple regression analysis was done to determine the predictors of percentage change in Tvol at 40 weeks. The regression of percentage change in Tvol at 40 weeks on group was significant ($p < 0.0001$). There was a significant effect (beyond group) of baseline thyroid volume, age, and ΔHb. Regression applied to bootstrapped data consistently selected group, baseline thyroid volume, age, and ΔHb as significant predictors for percentage change in Tvol (multiple $R^2 = 0.26$, $p < 0.0001$). Improvement in Hb from baseline to 40 weeks was a significant predictor of percentage change in Tvol at 40 weeks, suggesting iodine efficacy was greater in children who responded best to iron fortification (79). This study clearly showed that addition of iron to iodized salt improves the efficacy of iodine in goitrous children with a high prevalence of anemia. The high prevalence of overlapping iron and iodine deficiencies in this study (44% of children were both anemic and goitrous) argues strongly for a combined fortification strategy for this age group.

Dual Fortification of Salt with Potassium Iodate and Micronized Ferric Pyrophosphate

In the study described above (79), the DFS containing ferrous sulfate encapsulated with partially hydrogenated vegetable oil was efficacious. However, despite encapsulation, the ferrous sulfate produced a yellow color change in the DFS when salt moisture content was high. Commercially available forms of encapsulated ferrous sulfate and ferrous fumarate cause unacceptable color changes when added to low-grade salt in Africa (62).

Poorly soluble iron compounds, such as elemental iron powders or iron phosphates, tend to cause fewer sensory changes in foods (35). Ferric pyrophosphate

(FePP) has a white color and produces negligible color change when added to local salt in West and North Africa (62). When FePP is added to salt containing potassium iodate (KIO3), iodine stability is comparable to that of iodized salt (62). Although most commercial forms of FePP have a relative bioavailability ≤50% of ferrous sulfate (33, 35), reducing the particle size of FePP increases its absorption. In rats, the relative bioavailability (RBV) of FePP with a mean particle size of 2.5 μm is ≈70% that of ferrous sulfate (63). Micronized FePP may therefore have excellent potential as a fortificant in a DFS.

To test a DFS containing micronized ferric pyrophosphate, a second intervention study was done in rural northern Morocco. (77). Local salt was fortified with 25 μg iodine/g salt (as potassium iodate) and 2 mg iron/g salt (as micronized ferric pyrophosphate). This FePP contains 21% iron and has a mean particle size (d50) of 2.5 μm (d10, 0.4 μm; d90, 6.1 μm). After storage and acceptability trials, the efficacy of the DFS was compared with IS in a 10-month, randomized, double-blind trial in iodine-deficient 6- to 15-year-old children (n = 158) with a high prevalence of anemia. Per capita salt intakes in school-age children in this region are 7–12 g/day, and iron bioavailability from the local diet is estimated to be 2%–4% when adjusted for low body-iron stores (72).

All children from two primary schools were invited to participate in the 10-month study; all accepted (n = 163) and were enrolled. At baseline, UIC, Hb, C-reactive protein (CRP), SF, ZnPP, TfR, and Tvol were measured. The children were randomized at the household level into two groups: One group was given the IS and the second group was given the DFS. Both the investigators and the households were blind to group assignment. Two kg of salt was supplied to the households at the beginning of each month for 10 months. The salt was dispensed directly to the head of the household from a central supply at the local health center. At 5 and 10 months, all baseline measures were repeated.

Of the 163 children who began the study, 158 completed it. During the efficacy trial, the DFS provided ≈18 mg/d of iron; iron absorption was estimated to be ≈2%. In the DFS group at 10 months, mean Hb increased by 16 g/L ($p < 0.01$), body iron stores were significantly increased ($p < 0.01$), and the prevalence of IDA was reduced from 30% to 5% ($p < 0.001$). There were no significant differences in median UIC between the two groups throughout the study (Table 8). In both groups, median UIC at 5 and 10 months was significantly increased compared with baseline ($p < 0.001$). At 10 months, median UI had increased to near the 100 μg/L cutoff value for risk of iodine deficiency (68). In both groups, mean Tvol at 5 and 10 months was significantly decreased compared with baseline ($p < 0.01$) and there was a significant decrease in goiter prevalence ($p < 0.01$). However, at 10 months, mean percentage decrease in Tvol was significantly greater ($p < 0.01$) and goiter prevalence was significantly lower ($p < 0.01$) in the DFS group at 10 months (77) (Table 8).

These two DFS studies demonstrate that a DFS containing iodine and iron can be an effective fortification strategy in rural Africa. Ferric pyrophosphate has clear advantages as a component of a DFS: It has a white color, produces negligible color

TABLE 8 Urinary iodine concentration (UIC), thyroid volume, and goiter prevalence in children receiving iodized salt (IS) (n = 83) or dual-fortified salt (DFS) containing iodine and micronized ferric pyrophosphate (n = 75) after 10 months. Data from Reference 77

	UIC (μg/L)		Thyroid volume (ml) Percentage change from baseline		Goiter prevalence[1]	
Month	**IS**	**DFS**	**IS**	**DFS**	**IS**	**DFS**
0	12 (2–70)	10 (3–121)	8.3 ± 3.4	8.5 ± 3.7	59 [70]	54 [72]
10	104 (22–1784)[2]	97 (17–1356)[2]	6.9 ± 2.2 −16.3 ± 7.4	5.9 ± 2.3[3,4] −29.6 ± 8.6[3,4]	42 [51]	29 [39]

Values are medians (ranges), means ± SD, or number [percentage].

[1]By logistic regression, group difference increased with time ($p < 0.01$, comparing time and treatment model relative to time only model).

[2,3]Significantly different from baseline: [2]$p < 0.0001$; [3]$p < 0.01$.

[4]Significantly different from IS: $p < 0.01$.

change, and does not affect iodine stability when added to low-grade, high-moisture salt in West and North Africa (62, 77). In Asian countries, such as Thailand and Vietnam, where fish sauce is used as a condiment rather than salt, efforts are under way to dual fortify fish sauce with iron and iodine (12).

SUMMARY

Our findings suggest that a high prevalence of iron deficiency among children in areas of endemic goiter may reduce the effectiveness of iodized salt programs. In developing countries, it is estimated that 40%–45% of school-age children are anemic; approximately 50% of the cases are due to iron deficiency. Children are also highly vulnerable to IDD and are one of the main target groups of iodized salt programs. IDA may have a greater impact on IDD than do the previously described goitrogens because of its high prevalence in vulnerable groups, such as infants, young children, and women of childbearing age.

These findings argue strongly for improving iron status in areas of overlapping deficiency, not only to combat anemia but also to increase the efficacy of iodine prophylaxis. The dual fortification of salt with iodine and iron may prove to be an effective and sustainable method to accomplish these important goals. Future studies should address the significance of the interaction of iron and iodine deficiencies during pregnancy. Research should also try to identify other heme-dependent enzymes, such as thyroid peroxidase, that may be impaired during iron deficiency with functional consequences. Also, new approaches to further improve the stability and bioavailability of iodine and iron in dual-fortified salt are needed.

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