

CLINICAL STUDY

Addition of microencapsulated iron to iodized salt improves the efficacy of iodine in goitrous, iron-deficient children: a randomized, double-blind, controlled trial

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Abstract

Objective: In many developing countries, children are at high risk for both goiter and anemia. Iron (Fe) deficiency adversely affects thyroid metabolism and reduces efficacy of iodine prophylaxis in areas of endemic goiter. The study aim was to determine if co-fortification of iodized salt with Fe would improve efficacy of the iodine in goitrous children with a high prevalence of anemia.

Design and methods: In a 9-month, randomized, double-blind trial, 6–15 year-old children ($n = 377$) were given iodized salt (25 µg iodine/g salt) or dual-fortified salt with iodine (25 µg iodine/g salt) and Fe (1 mg Fe/g salt, as ferrous sulfate microencapsulated with partially hydrogenated vegetable oil).

Results: In the dual-fortified salt group, hemoglobin and Fe status improved significantly compared with the iodized salt group ($P < 0.05$). At 40 weeks, the mean decrease in thyroid volume measured by ultrasound in the dual-fortified salt group (–38%) was twice that of the iodized salt group (–18%) ($P < 0.01$). Compared with the iodized salt group, serum thyroxine was significantly increased ($P < 0.05$) and the prevalence of hypothyroidism and goiter decreased ($P < 0.01$) in the dual-fortified salt group.

Conclusion: Addition of encapsulated Fe to iodized salt improves the efficacy of iodine in goitrous children with a high prevalence of anemia.

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Introduction

Despite substantial progress against the iodine deficiency disorders (IDD), it is estimated that 125 million people in Africa, or 20% of the population, remain iodine deficient and goitrous (1). The efficacy of salt iodization, the preferred strategy for IDD control (1, 2), may be influenced by multiple nutritional factors, including goitrogenic foods, protein–calorie malnutrition, and selenium deficiency (3–6). Iron (Fe) deficiency also impairs thyroid metabolism and may influence IDD. The two initial steps of thyroid hormone synthesis are catalyzed by Fe-dependent thyroid peroxidase (TPO). In rats, Fe-deficiency anemia sharply reduces TPO activity and decreases plasma thyroxine (T_4) and triiodothyronine (T_3) levels (7). Fe-deficiency anemia may also alter central nervous system control of thyroid metabolism (8), modify nuclear T_3 binding (9), reduce peripheral conversion of T_4 to T_3 (8) and increase circulating thyrotropin (TSH) (8, 10). In

goitrous children, the therapeutic response to oral iodized oil is impaired in children with Fe-deficiency anemia compared with Fe-sufficient children (11). In addition, Fe supplementation of goitrous, Fe-deficient children improves their response to oral iodized oil and iodized salt (12, 13).

In the mountains of northern Morocco, the goiter rate among schoolchildren is 53–64% and 25–35% suffer from Fe-deficiency anemia (14, 15). Salt is likely to be an effective vehicle for fortification, as it is widely and regularly consumed at a level of 5–12 g/day (16). Thus, the dual fortification of salt with iodine and Fe could be a sustainable method to prevent both iodine and Fe deficiencies. However, ensuring the stability and bioavailability of Fe and iodine in dual-fortified salt is difficult (17–20). 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 . Ferrous Fe is readily oxidized to the generally less bioavailable ferric

form (21), and both ferric and ferrous Fe can combine with impurities in the salt to give unacceptable yellow or brown off-colors (20). Placing a physical barrier around the Fe could prevent these adverse interactions. Based on this idea, we added Fe as microencapsulated ferrous sulfate to iodized salt. Because Fe-deficiency anemia adversely affects thyroid metabolism and may reduce the efficacy of iodine prophylaxis, the aim of this study was to determine if co-fortification of iodized salt with Fe would improve the efficacy of iodine in the salt in iodine-deficient Moroccan schoolchildren with a high prevalence of Fe-deficiency anemia.

Subjects and methods

The study was carried out in the Brikcha Rural Commune, an area of endemic goiter (14, 15) in the Rif mountains of northern Morocco. Salt is supplied by a local cooperative and is not iodized, and has a native iodine content <2 ppm (15). We directly measured salt intake using 3-day weighed food records in 50 households randomly selected from local census rolls during the damp and dry seasons. Mean salt intake (S.D.) for adult males and females was 12.1(2.9) and 9.7(2.3) g/day respectively. For 6–15 year-old children, salt intake was 7.3 to 11.6 g/day.

The subjects were 6–15 year-old children from two neighboring primary schools. All children in the schools were invited to participate in the study, all accepted ($n = 377$) and were enrolled. Informed oral consent was obtained from the chief medical officer of the province, the school director, and the parents of the children. The University Children's Hospital in Zürich and the Ministry of Health in Morocco gave ethical approval for the study.

At baseline, weight and height were measured (22) and a casual spot urine sample was collected for measurement of urinary iodine (UI). Thyroid gland volume was measured using a portable Aloka SSD-500 Echocamera (Aloka, Mure, Japan) with a high-resolution 7.5 MHz linear transducer (23). Whole blood was collected by venipuncture for determination of hemoglobin (Hb), ferritin (SF), zinc protoporphyrin (ZnPP), and transferrin receptor (TfR). Blood was spotted onto filter paper for measurement of TSH and T_4 .

Because each participating family shared a monthly salt portion (see below), the children were randomized at the household level into two groups. One group was provided salt fortified with iodine alone while the second group was provided with salt dual fortified with iodine and Fe. Both the investigators and the households were blind to group assignment. The native, non-iodized salt produced by the local cooperative was used to prepare the fortified salts. The iodine was added as analytical reagent grade potassium iodide (KI) (Sigma & Aldrich, Buchs, Switzerland) at a level of 25 μg I/g salt. The Fe was added as ferrous

sulfate hydrate microencapsulated with partially hydrogenated vegetable oil (50% substrate) (Cap-Shure FS-165E-50, Balchem, Slate Hill, NY, USA) at a fortification level of 1 mg Fe/g salt. The Fe and iodine were dry mixed into the salt using an electric rotating drum mixer (ELTE 650, Engelsmann, Ludwigshafen, Germany) at 30 r.p.m. for 10 min. We chose the fortification level based on salt intake data from Brikcha of 7–12 g/day in children aged 6–15 years, and anticipated a 20% loss of iodine during storage and cooking. Thus, both salts were fortified to provide ~ 150 –250 μg I/day, and the Fe level in the dual fortified salt was set to provide ~ 7 –12 mg of Fe/day. Based on mean per capita salt intake of 6–14 g/day in the total population and local census data indicating an average of 7.5 individuals per household, each household was provided with 2 kg fortified salt at the beginning of each month for 9 months. The salt was dispensed directly to the head of the household from a central supply at the local health center.

At 10, 20 and 40 weeks, weight and height were remeasured and spot urine samples were collected for measurement of UI. Whole blood was spotted onto filter paper for determination of T_4 and TSH. Thyroid volume was measured using ultrasound. At 20 and 40 weeks, whole blood was collected by venipuncture for determination of Hb, SF, ZnPP, and TfR. For monitoring, 50 g aliquots ($n = 6$) of the salts were taken and measured for I content at each monthly mixing, and for Fe content at 1, 3, and 9 months. On completion of the study, children who remained Fe-deficient anemic were treated with oral Fe (60 mg Fe as ferrous sulfate 4 days/week for 12 weeks).

Laboratory analyses

Urine and blood samples were transported on ice to the provincial hospital laboratory. Serum and urine samples were aliquoted and frozen at -20°C until analysis. UI was measured using a modification of the Sandell-Kolthoff reaction (24). At UI concentrations of 47 $\mu\text{g}/\text{l}$ and 79 $\mu\text{g}/\text{l}$, the coefficients of variation of this assay in our laboratory are 10.3 and 12.7% respectively. The limit of detection is 2 $\mu\text{g}/\text{l}$; samples below this limit were assigned a value of zero. Dried blood spots on filter paper were analyzed for whole blood TSH and serum T_4 using immunoassay (25). Normal reference values are <3.5 mU/l for whole blood TSH and 65–165 nmol/l for serum T_4 . Hb was measured using an AcT8 Counter (Beckman Coulter, Krefeld, Germany). ZnPP was measured on washed red blood cells using a hematofluorometer (Aviv Biomedical, Lakewood, NJ, USA). SF and TfR were measured using an enzyme-linked immunosorbent assay (26, 27). Normal reference values are: SF, 12–300 $\mu\text{g}/\text{l}$; TfR, 2.9–8.5 mg/l; ZnPP, <40 $\mu\text{mol}/\text{mol}$ heme. Salt I content was measured in 10 g salt aliquots dissolved in distilled water using a modification of the

Sandell–Kolthoff reaction (24). Fe concentration of the salt was measured using atomic absorption spectroscopy (Varian Techtron Pty Ltd, Mulgrave Victoria, Australia). Fe deficiency was defined as either SF < 12 µg/l or TfR > 8.5 mg/l+ZnPP > 40 µmol/mol heme (28). Anemia was defined as Hb < 120 g/l in children aged ≥ 12 years, and Hb < 115 g/l in children aged 6–11 years (29). Thyroid volume was calculated using the method of Brunn *et al.* (30). MZ performed all ultrasound measurements during the study. To estimate intraobserver variability, duplicate thyroid volume measurements were carried out in 25 children at the 10 and 40 week visits; the mean (s.d.) variability was 3.7 (2.0)%. Updated World Health Organization/International Council for the Control of Iodine Deficiency Disorders (WHO/ICCIDD) normative values for thyroid volume in school-age children according to sex and body surface area (BSA) were used to define goiter (31).

Statistical analyses

Data processing and statistics were carried out using SPLUS 2000 (Mathsoft, Seattle, WA, USA), Prism3 (GraphPad, San Diego, CA, USA) and Excel (Microsoft, Seattle, WA, USA). Normally distributed data were expressed as means (s.d.) and were compared by Student's *t*-test. Parameters not normally distributed were expressed as medians and ranges, and were compared by Wilcoxon or Mann-Whitney tests. To reduce the effects of variability among individuals, percentage change in thyroid volume from baseline (% ΔT_{vol}) was calculated for each child before deriving means. A 2-factor repeated measures ANOVA was carried out to compare effects of time and group and time by group

for Hb, SF, TfR, ZnPP, UI, TSH, T_4 , thyroid volume, and % ΔT_{vol} . If the interaction effect was significant, individual means were compared using *t*-tests between groups and paired *t*-tests within groups and adjusted for multiple comparisons (Bonferroni correction). Proportions were compared using the chi-square test. Logistic regression was carried out to compare effects of time and group and time by group for the binary variables of Fe-deficiency anemia, goiter and hypothyroidism. Multiple regression was used to test for associations. Significance was set at $P < 0.05$.

Results

Table 1 compares the iodized salt and dual-fortified salt groups at baseline. There were no significant differences in measured baseline characteristics between groups. Of the 377 children who began the study, 367 completed it; 9 children moved away (4 in the iodized salt group, 5 in the dual-fortified salt group) and one child in the iodized salt group refused further venipuncture. In the monitoring aliquots of salt taken at mixing at 1, 3, 6, and 9 months ($n = 24$), the mean I concentrations (s.d.) in the iodized salt and dual-fortified salt were 22.9 (3.0) and 23.4 (3.1) µg I/g salt respectively. There was no significant difference in mean I concentration between the salts at any of the time points (data not shown). The mean Fe concentration (s.d.) in the dual-fortified salt measured at 0, 3, and 9 months ($n = 18$) was 0.9 (0.3) mg Fe/g salt.

As shown in Table 2, compared with the iodized salt group, mean Hb was significantly increased and was greater in the dual-fortified salt group at 40 weeks ($P < 0.02$). The prevalence of Fe-deficiency anemia was sharply lower in the dual-fortified salt group at 40

Table 1 Baseline parameters of the children in the iodized salt (IS) and dual fortified salt (DFS) groups. Results are expressed as means \pm s.d., medians (range) or number of children [%].

Parameters	IS ($n = 184$)	DFS ($n = 183$)
Age (years)	10.0 \pm 2.4	10.4 \pm 2.5
Sex (F/M)	85/99	89/94
BMI (kg/m ²)	15.9 \pm 1.7	16.2 \pm 1.8
Hemoglobin (g/l)	111 \pm 14	113 \pm 13
Serum ferritin (µg/l)	23 \pm 18	20 \pm 16
Serum transferrin receptor (mg/l)	8.2 (4.4–82.6)	8.7 (4.3–77.1)
Whole-blood zinc protoporphyrin (µmol/mol heme)	63 \pm 47	63 \pm 47
Prevalence of iron-deficiency anemia	66 [36]	64 [35]
Urinary iodine (µg/l)	18 (0–127)	16 (0–143)
Urinary iodine (%)		
< 20 µg/l	58	59
< 50 µg/l	87	89
< 100 µg/l	95	96
Whole blood TSH (mU/l)	0.8 (0.4–6.2)	0.9 (0.4–27.0)
Serum T_4 (nmol/l)	82.1 \pm 17.3	82.8 \pm 19.8
Prevalence of hypothyroidism (serum T_4 < 65 nmol/l)	35 [19]	37 [20]
Thyroid volume (ml)	8.9 \pm 3.4	9.1 \pm 3.7
Prevalence of goiter	133 [72]	129 [70]

There were no significant differences in baseline parameters between groups. BMI, body mass index.

Table 2 Change in hemoglobin and prevalence of iron deficiency anemia in the iodized salt (IS) ($n = 184$) and dual-fortified salt (DFS) ($n = 183$) groups over 40 weeks. Results are means \pm s.d. (hemoglobin) or number of children [%] (prevalence of iron-deficiency anemia).

Time	Hemoglobin (g/l) ^a		Prevalence of iron-deficiency anemia ^b	
	IS	DFS	IS	DFS
Baseline	111 \pm 14	113 \pm 13	66 [36]	64 [35]
20 weeks	115 \pm 14	116 \pm 13	52 [28] ^g	51 [28] ^c
40 weeks	116 \pm 12	127 \pm 12 ^{c,e}	56 [30] ^h	15 [8] ^{d,f}

^aSignificant treatment \times time interaction, $P < 0.01$ (ANOVA).

^bPrevalence of iron-deficiency anemia was significantly decreased in the DFS group: $P < 0.001$ comparing time and group model relative to time only model (logistic regression).

^c $P < 0.01$, ^d $P < 0.001$: significantly different from baseline of DFS group;

^e $P < 0.02$, ^f $P < 0.001$: significantly different from IS group at 40 weeks;

^g $P < 0.01$, ^h $P < 0.05$: significantly different from baseline of IS group.

weeks ($P < 0.001$). Table 3 shows the change in thyroid volume in the two groups. At 40 weeks, mean thyroid volume in the dual-fortified salt group was significantly decreased compared with baseline ($P < 0.001$) and compared with the iodized salt group ($P < 0.05$). At 40 weeks, the mean $\% \Delta T_{vol}$ from baseline (s.d.) in the dual-fortified salt and iodized salt groups was $-37.8 \pm 9.1\%$ and $-18.0 \pm 6.6\%$ respectively ($P < 0.01$). At 40 weeks, the goiter rate was significantly decreased in the dual-fortified salt group compared with the iodized salt group ($P < 0.001$). As modeled by logistic regression, the probability of goiter was significantly reduced in the dual-fortified salt group compared with the iodized salt group, and the group difference increased with time ($P < 0.01$ comparing time and group model relative to time only model) (Fig. 1).

Table 3 Thyroid volume and change in thyroid volume from baseline in the iodized salt (IS) and dual-fortified salt (DFS) groups over 40 weeks. Results are means \pm s.d.

Thyroid volume	IS ($n = 184$)	DFS ($n = 183$)
Baseline (ml)	8.9 \pm 3.4	9.1 \pm 3.7
10 weeks (ml)	8.7 \pm 3.9	9.1 \pm 2.8
Percentage change from baseline	-2.9 ± 12.4	-1.4 ± 11.9
20 weeks (ml)	8.3 \pm 2.7	7.5 \pm 3.4 ^c
Percentage change from baseline	-6.2 ± 11.6	-16.9 ± 11.1 ^{d,f}
40 weeks (ml)	7.3 \pm 2.4 ^a	5.7 \pm 2.1 ^{e,g}
Percentage change from baseline	-18.0 ± 6.6 ^b	-37.8 ± 9.1 ^{e,h}

There is a significant treatment \times time interaction: $P < 0.01$ (ANOVA) for thyroid volume and change in thyroid volume from baseline.

^a $P < 0.02$, ^b $P < 0.05$: significantly different from baseline of IS group;

^c $P < 0.02$, ^d $P < 0.05$, ^e $P < 0.001$: significantly different from baseline of DFS group;

^f $P < 0.05$, ^g $P < 0.05$: significantly different from IS group at 20 weeks;

^h $P < 0.05$, ⁱ $P < 0.01$: significantly different from IS group at 40 weeks.

Table 4 shows the changes in UI, TSH, and T_4 in the two groups. There were no significant differences in median UI between the two groups throughout the study. At 20 and 40 weeks median UI was well above the WHO/ICCIDD cut-off value (100 μ g/l) for risk of iodine deficiency (1). There was a non significant decrease in median TSH in both groups over the course of the study (at 40 weeks compared with baseline, $P = 0.063$ in the iodized salt group; $P = 0.061$ in the dual-fortified salt group); median TSH was within the normal range in both groups throughout the study. Mean serum T_4 increased significantly from baseline in the dual-fortified salt group ($P < 0.02$) and was significantly greater than in the iodized salt group at 20 and 40 weeks ($P < 0.05$). At 20 and 40 weeks, the prevalence of hypothyroidism ($T_4 < 65$ nmol/l) was significantly reduced in the dual-fortified salt group compared with the iodized salt group

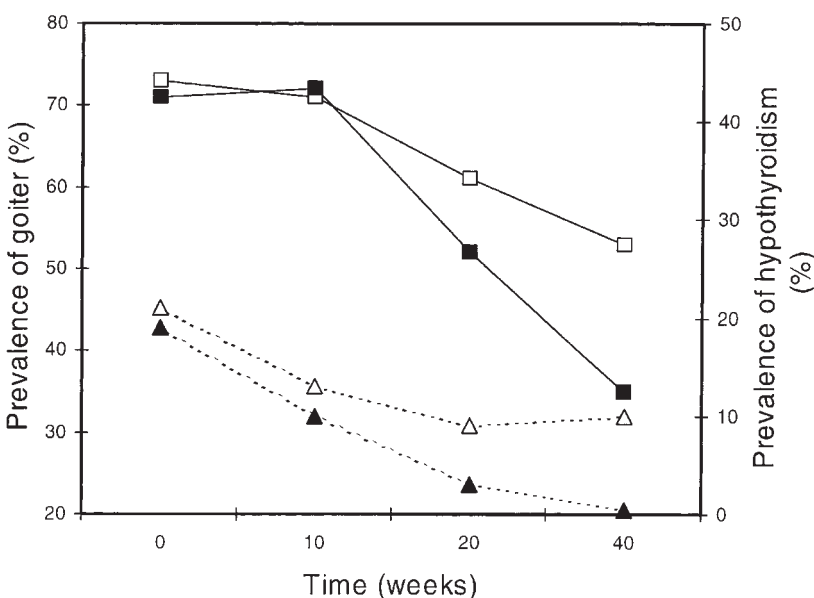


Figure 1 By logistic regression, the probability of goiter (squares) and hypothyroidism (triangles) was significantly reduced in the children receiving dual-fortified salt containing iron and iodine ($n = 183$) (solid symbols), compared with the group receiving iodized salt ($n = 184$) (open symbols). For both, the group difference increased with time ($P < 0.01$, comparing time and group model relative to time only model).

Table 4 Concentrations of serum thyroxine (means \pm s.d.), whole-blood thyrotropin and urinary iodine (medians (range)), and distribution of urinary iodine (percentages) in the iodized salt (IS) ($n = 184$) and dual-fortified salt (DFS) ($n = 183$) groups over 40 weeks.

Time (weeks)	Serum thyroxine (nmol/l) ^a		Whole blood thyrotropin (mU/l)		Urinary iodine (μ g/l)		Urinary iodine < 20 μ g/l / < 50 μ g/l / < 100 μ g/l	
	IS	DFS	IS	DFS	IS	DFS	IS	DFS
Baseline	82.1 \pm 17.3	82.8 \pm 19.8	0.9 (0.4–6.2)	0.9 (0.4–27.0)	18 (0–127)	16 (0–143)	58/87/95	59/89/96
10	91.4 \pm 23.8	96.6 \pm 24.3	1.0 (0.3–2.9)	0.9 (0.3–3.2)	79 ^f (12–488)	87 ^c (19–511)	4/22/53	5/19/51
20	89.8 \pm 19.9	103.5 \pm 20.2 ^{b,d}	1.2 (0.4–14.9)	1.1 (0.3–8.6)	179 ^f (22–432)	183 ^c (31–529)	2/14/28	3/12/31
40	85.3 \pm 12.7	102.2 \pm 17.4 ^{b,e}	0.6 (0.3–1.9)	0.7 (0.2–2.4)	182 ^f (14–474)	189 ^c (23–406)	4/11/24	3/12/26

^aSignificant treatment \times time interaction, $P < 0.01$ (ANOVA).

^b $P < 0.02$, ^c $P < 0.001$: significantly different from baseline of DFS group; ^d $P < 0.05$: significantly different from IS group at 20 weeks; ^e $P < 0.05$: significantly different from IS group at 40 weeks; ^f $P < 0.001$: significantly different from baseline of IS group.

($P < 0.001$). Of the 72 children who had low total T_4 at baseline, only 16 had an elevated TSH. We have found a similar high prevalence of normal TSH together with low total T_4 in children in a severely iodine-deficient region of Côte d'Ivoire (11). By logistic regression, the probability of hypothyroidism was significantly decreased in the dual-fortified salt group compared with the iodized salt group, and the group difference increased with time ($P < 0.01$ comparing time and group model relative to time only model) (Fig. 1).

Multiple regression of $\% \Delta T_{vol}$ at 40 weeks on group, baseline characteristics in Table 1, and change in Hb from baseline to 40 weeks (ΔHb) was carried out. The regression of $\% \Delta T_{vol}$ 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 $\% \Delta T_{vol}$ (multiple $R^2 = 0.26$, $P < 0.0001$).

Discussion

The children in this region suffer from widespread and severe deficiencies of Fe and iodine. Over half of the children were Fe deficient – 36% had Fe-deficiency anemia and an additional 17% were Fe deficient without anemia. The children were also severely iodine deficient: median UI was only 17 μ g/l, the goiter rate measured by ultrasound was 71%, and 1 in 5 children had low serum T_4 concentrations, suggesting hypothyroidism due to iodine deficiency (Table 1). Forty-four percent of children were suffering from both goiter and Fe deficiency. The high prevalence of overlapping Fe and I deficiencies in this study and others (11, 14,

15) argues strongly for a combined fortification strategy for this age group.

The dual-fortified salt was an effective vehicle for delivery of Fe, providing ~ 7 –12 mg of additional dietary Fe per day, sharply improving Fe status, and reducing the prevalence of Fe-deficiency anemia from 35% to 8% after 40 weeks (Table 2). Iodine absorption from the salts appeared comparable: throughout the study, median UI was not significantly different between the two groups, and both groups, as indicated by median UI $> 100 \mu$ g/l, were iodine sufficient after the 20th week (Table 4).

The addition of Fe to the iodized salt significantly improved efficacy of the iodine. Both anatomic and biochemical measures indicated a marked improvement in thyroid function in the dual-fortified salt group compared with the iodized salt group (Tables 3 and 4). After 40 weeks, the mean decrease in thyroid volume from baseline ($\% \Delta T_{vol}$) in the dual-fortified salt group was twice that in the iodized salt group. This was reflected in the sharp difference in the goiter rates between the groups at 20 and 40 weeks (Fig. 1). Thyroid hormone status significantly improved in the dual-fortified salt group compared with the iodized salt group: at 20 and 40 weeks, mean T_4 was increased and the prevalence of hypothyroidism was decreased in the dual-fortified salt group (Table 4). By regression, improvement in Hb from baseline to 40 weeks was a significant predictor of $\% \Delta T_{vol}$ at 40 weeks. This suggests iodine efficacy was greater in children who responded best to Fe fortification.

These data agree with results from our previous studies in goitrous, Fe-deficient children in West Africa. In Côte d'Ivoire, the efficacy of oral iodized oil was impaired in children with Fe-deficiency anemia compared with Fe-sufficient, non anemic children (11). In an open, uncontrolled trial, Fe treatment of

goitrous children with Fe-deficiency anemia improved their response to oral iodized oil (12). In a randomized trial of oral Fe supplementation compared with placebo in children receiving iodized salt, Fe treatment significantly increased the efficacy of iodized salt (13).

Fe deficiency may influence iodine and thyroid metabolism in several ways. In animal studies, Fe-deficiency anemia decreases circulating concentrations of T_3 and T_4 by 20–40% (7, 8). Fe-deficiency anemia also reduces activity of hepatic thyroxine-5-deiodinase, and thereby impairs peripheral conversion and activation of T_4 to T_3 (8). Fe-deficiency anemia may also modify nuclear T_3 binding (9). The effects of Fe deficiency on the thyrotropin releasing hormone (TRH)–TSH axis are equivocal: although Fe-deficiency anemia appears to blunt the TSH response to TRH (8), some studies have found an increase in circulating TSH concentrations in Fe-deficiency anemia (10), while others have reported no change or a decrease in TSH (7, 8). In human studies, compared with healthy controls, Fe-deficient adults have lower circulating T_4 and T_3 levels and may have higher TSH concentrations (10, 32). New data from our laboratory suggest that impairment of TPO, an Fe-dependent enzyme, may also play a role (7). TPO catalyzes the initial steps of thyroid hormone synthesis - iodide incorporation into tyrosine residues of thyroglobulin and covalent bridging of the residues. In rats, Fe-deficiency anemia sharply reduces TPO activity and lowers circulating T_3 and T_4 levels (7). In many of the children in this study, Fe deficiency may have decreased TPO activity and impaired thyroid hormone synthesis in response to iodine.

Our findings suggest that a high prevalence of Fe 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 (33), of which approximately 50% is due to Fe deficiency. Children are also highly vulnerable to IDD and are one of the main target groups of iodized salt programs (1, 2). These deficiencies often coexist - this study and previous surveys in West and North Africa have found that 20–35% of school-age children suffer from both goiter and Fe deficiency (11, 15). Our findings argue strongly for improving Fe 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 Fe may prove to be an effective and sustainable method to accomplish these important goals.

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References

- 1 World Health Organization, United Nations Children's Fund & International Council for the Control of Iodine Deficiency Disorders. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination*, WHO/NHD/01.1. Geneva: WHO, 2001.
- 2 World Health Organization, United Nations Children's Fund & International Council for the Control of Iodine Deficiency Disorders. *Indicators for Assessing Iodine Deficiency Disorders and their Control through Salt Iodination*, WHO/NUT/94.6. Geneva: WHO, 1994.
- 3 Boyages SC. Iodine deficiency disorders. *Journal of Clinical Endocrinology and Metabolism* 1993 **77** 587–591.
- 4 Thilly CH, Vanderpas JB, Bebe N, Ntambue K, Contempré B, Swennen B *et al.* Iodine deficiency, other trace elements and goitrogenic factors in the etiopathology of iodine deficiency disorders. *Biological Trace Element Research* 1992 **32** 229–243.
- 5 Zimmermann MB, Torresani T, Adou P, Zeder C & Hurrell RE. Effect of oral iodized oil on thyroid size and thyroid hormone metabolism in children with concurrent selenium and iodine deficiency. *European Journal of Clinical Nutrition* 2000 **54** 209–213.
- 6 Hurrell RE. Bioavailability of iodine. *European Journal of Clinical Nutrition* 1997 **51** S9–S12.
- 7 Hess SY, Zimmermann MB, Arnold M, Langhans W & Hurrell RE. Iron-deficiency anemia reduces thyroid peroxidase activity in rats. *Journal of Nutrition* 2002 **132** 1951–1955.
- 8 Beard JL, Brigham DE, Kelley SK & Green MH. Plasma thyroid hormone kinetics are altered in iron-deficient rats. *Journal of Nutrition* 1998 **128** 1401–1408.
- 9 Smith SM, Finley J, Johnson LK & Lukaski HC. Indices of *in vivo* and *in vitro* thyroid hormone metabolism in iron-deficient rats. *Nutrition Research* 1994 **14** 729–739.
- 10 Beard JL, Borel MJ & Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. *American Journal of Clinical Nutrition* 1990 **52** 813–819.
- 11 Zimmermann MB, Adou P, Zeder C, Torresani T & Hurrell RE. Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in the Côte d'Ivoire. *American Journal of Clinical Nutrition* 2000 **71** 88–93.
- 12 Zimmermann MB, Adou P, Torresani T, Zeder C & Hurrell RE. Iron supplementation in goitrous, iron-deficient children improves their response to oral iodized oil. *European Journal of Endocrinology* 2000 **142** 217–223.
- 13 Hess SY, Zimmermann MB, Adou P, Torresani T & Hurrell RE. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Côte d'Ivoire. *American Journal of Clinical Nutrition* 2002 **75** 743–748.
- 14 Chaouki N, Ottmani S, Saad A, Hamdaoui ME, Benabdejlil C, Kadiri A *et al.* The prevalence of iodine deficiency disorders in

- children 6–12 yrs old in Morocco. *Bulletin Epidémiologique Maroc* 1996 **1** 2–23.
- 15 Zimmermann MB, Saad A, Hess SY, Torresani T & Chaouki N. Thyroid ultrasound compared with WHO 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency. *European Journal of Endocrinology* 2000 **143** 727–731.
 - 16 Alaoui, L. *Iron Intake, Sources and Bioavailability in Chefchaouen Province, Morocco*. PhD thesis, University of Oregon.
 - 17 Madhavan Nair K, Brahman GNV, Ranganathan S, Vijayaraghavan K, Sivakumar B & Krishnaswamy K. Impact evaluation of iron and iodine-fortified salt. *Indian Journal of Medical Research* 1998 **108** 203–211.
 - 18 Sattarzadeh M & Zlotkin SH. Iron is well absorbed by healthy adults after ingestion of double-fortified table salt and urinary excretion is unaffected. *Journal of Nutrition* 1999 **129** 117–121.
 - 19 Sivakumar B, Brahman GNV, Nair KM, Ranganathan S, Vishnuvardhan Rao M, Vijayaraghavan K *et al.* Prospects of fortification of salt with iron and iodine. *British Journal of Nutrition* 2001 **85** S167–S173.
 - 20 Mannar MG & Diosady LL. Double fortification of salt with iron and iodine. In *Food Fortification to End Micronutrient Malnutrition*, pp 89–94. Ottawa: The Micronutrient Initiative, 1998.
 - 21 Hurrell RE. Bioavailability of iron. *European Journal of Clinical Nutrition* 1997 **51** S4–S8.
 - 22 World Health Organization. *Physical Status: The Use and Interpretation of Anthropometry*, pp 427–429. Geneva: WHO, 1995.
 - 23 Zimmermann MB, Molinari L, Spehl M, Weidinger-Toth J, Podoba J, Hess SY *et al.* Toward a consensus on reference values for thyroid volume in iodine-replete schoolchildren: results of a workshop on interobserver and interequipment variation in sonographic measurement of thyroid volume. *European Journal of Endocrinology* 2001 **144** 213–220.
 - 24 Pino S, Fang SL & Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. *Clinical Chemistry* 1996 **42** 239–243.
 - 25 Torresani T & Scherz R. Thyroid screening of neonates without use of radioactivity: evaluation of time-resolved fluoroimmunoassay of thyrotropin. *Clinical Chemistry* 1986 **32** 1013–1016.
 - 26 Flowers CH, Kuizon M, Beard J, Skikne B, Covell A & Cook JD. A serum ferritin assay for prevalence studies of iron deficiency. *American Journal of Hematology* 1986 **23** 141–151.
 - 27 Skikne BS, Flowers CH & Cook JD. Serum transferrin receptor: a quantitative measure of tissue iron deficiency. *Blood* 1990 **75** 1870–1876.
 - 28 Cook JD, Baynes RD & Skikne BS. Iron deficiency and the measurement of iron status. *Nutrition Research Reviews* 1992 **5** 189–202.
 - 29 United Nations Children's Fund/World Health Organization/United Nations University/ Micronutrient Initiative Technical Workshop. *Preventing Iron Deficiency in Women and Children: Background and Consensus on Key Technical Issues and Resources for Advocacy, Planning and Implementing National Programmes*, pp 10. Canada: International Nutrition Foundation, 1998.
 - 30 Brunn J, Block U, Ruf G, Bos I, Kunze WP & Scriba PC. Volume measurement of the thyroid gland using real-time sonography. *Deutsches Medizinisches Wochenschrift* 1981 **106** 1338–1340.
 - 31 Zimmermann MB, Molinari L, Spehl M, Weidinger-Toth J, Podoba J, Hess SY *et al.* Updated provisional WHO/ICCIDD reference values for sonographic thyroid volume in iodine-replete school-age children. *International Council for the Control of the Iodine Deficiency Disorders Newsletter* 2001 **1** 12.
 - 32 Dillman E, Gale C, Green W, Johnson DG, Mackler B, Finch C *et al.* Hypothermia in iron deficiency due to altered triiodothyronine metabolism. *American Journal of Physiology* 1984 **239** R377–R381.
 - 33 World Health Organization/United Nations Children's Fund/United Nations University. *IDA: Prevention, Assessment and Control. Report of a joint WHO/UNICEF/UNU consultation*, pp 1–9. Geneva: WHO, 1998.

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