Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Côte d’Ivoire1–3

Sonja Y Hess, Michael B Zimmermann, Pierre Adou, Toni Torresani, and Richard F Hurrell

ABSTRACT

Background: In many developing countries, children are at high risk of both goiter and iron deficiency anemia. Iron deficiency adversely affects thyroid metabolism and may reduce the efficacy of iodine prophylaxis in areas of endemic goiter.

Objective: The aim of this study was to determine whether iron supplementation in goitrous, iron-deficient children would improve their response to iodized salt.

Design: We conducted a randomized, double-blind, placebo-controlled trial in 5–14-y-old children in Côte d’Ivoire. Goitrous, iron-deficient children (n = 166) consuming iodized salt (10–30 mg I/kg salt at the household level) were supplemented with either iron (60 mg Fe/d, 4 d/wk for 16 wk) or placebo. At 0, 1, 6, 12, and 20 wk, we measured hemoglobin, serum ferritin, serum transferrin receptor, whole-blood zinc protoporphyrin, thyrotropin, thyroxine, urinary iodine, and thyroid gland volume (by ultrasonography).

Results: Hemoglobin and iron status at 20 wk were significantly better after iron treatment than after placebo (P < 0.05). At 20 wk, the mean reduction in thyroid size in the iron-treated group was nearly twice that in the placebo group (–22.8 ± 10.7% compared with –12.7 ± 10.1%; P < 0.01). At 20 wk, goiter prevalence was 37% in the iron-treated group compared with 62% in the placebo group (P < 0.02). There were no significant differences between groups in whole-blood thyrotophin or serum thyroxine at baseline or during the intervention.

Conclusions: Iron supplementation improves the efficacy of iodized salt in goitrous children with iron deficiency. A high prevalence of iron deficiency among children in areas of endemic goiter may reduce the effectiveness of iodine prophylaxis.


KEY WORDS  Iodine, iron, deficiency, anemia, goiter, iodized oil, iodized salt, children, Côte d’Ivoire

INTRODUCTION

Iodine deficiency produces a spectrum of disorders—endemic goiter, hypothyroidism, cretinism, and congenital anomalies—that are termed the iodine deficiency disorders (IDDs) (1). In Africa, 124 million persons—20% of the population—are affected by goiter (2). Universal salt iodization is the preferred strategy for IDD control (1). In iodine-deficient areas, multiple nutritional factors, including goitrogenic foods, protein-energy malnutrition, and selenium deficiency, may influence the prevalence and severity of IDD and modify the response to iodine prophylaxis (3–5).

Iron status also affects thyroid metabolism and IDD. The 2 initial steps of thyroid hormone synthesis are catalyzed by thyroperoxidases and are dependent on iron. In addition, iron deficiency may alter central nervous system control of thyroid metabolism (6) and modify nuclear triiodothyronine binding (7). Iron-deficiency anemia decreases plasma concentrations of thyroxine and triiodothyronine, reduces the peripheral conversion of thyroxine to triiodothyronine, and increases circulating concentrations of thyrotophin (6, 8, 9). In goitrous children, the therapeutic response to orally given iodized oil is lower in children with iron deficiency anemia than in iron-sufficient children (10). In addition, in an open, uncontrolled trial, iron treatment of goitrous children with iron deficiency anemia improved their response to orally given iodized oil (11).

Deficiencies of iron and iodine are major overlapping public health problems in the developing world, and many children are at high risk of both goiter and iron deficiency anemia. In western Côte d’Ivoire, 30–50% of school-aged children are goitrous and 37–47% are iron deficient (11). Therefore, the aim of this study was to determine whether iron treatment would increase the efficacy of iodized salt and oral iodized oil in children with both goiter and iron deficiency.

SUBJECTS AND METHODS

The study was conducted in 9 primary schools of the Danané Health District, an area of endemic goiter in the mountains of western Côte d’Ivoire (11). The University Children’s Hospital in

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Zürich, Switzerland, and the Ministry of Research of Côte d’Ivoire gave ethical approval for the study. Informed oral consent was obtained from the village chiefs and the children’s teachers and families. In 1997 the median urinary iodine concentration and the goiter rate by palpation in school-aged children in this region were 28 µg/L and 45%, respectively (11), indicating moderate-to-severe IDD (1). Côte d’Ivoire began a universal salt iodization program in 1997 at a production level of 30–50 µg/g. In late 1998, iodized salt was introduced into the Danané region. Access to iodized salt in this region had steadily increased; by November 1999, it was estimated that >80% of households were using iodized salt at a household level of 20–30 µg/g (P Adou, National Institute of Public Health of Côte d’Ivoire, unpublished observations, 2000). The present study was conducted from November 1999 through June 2000.

Screening study

All children in the 9 schools were screened (n = 1014). Weight and height were measured, and spot urine samples were collected for the measurement of urinary iodine. Thyroid gland volume was measured with an Aloka SSD-500 Echocamera (Aloka, Mure, Japan) with a high-resolution 7.5-MHz linear transducer (12). Measurements were performed on subjects sitting upright with the neck extended. Blood was collected by venipuncture for the measurement of hemoglobin, whole-blood zinc protoporphyrin, serum ferritin, and serum transferrin receptor (TfR). Blood was spotted onto filter paper for the measurement of thyrotropin and thyroxine. Random salt samples (n = 213) from households of children in the screening study were collected to measure iodine concentration.

Intervention study

All children from the screening study who were both goitrous and iron deficient (as defined by the criteria described below) were invited to join a double-blind intervention study. Children with hemoglobin concentrations < 80 g/L were excluded and were treated with oral iron. The remaining children (n = 169) were randomly assigned to 2 groups. One group received oral ferrous sulfate (60 mg elemental Fe) as 4 tablets/wk for 16 wk; the second group received identical-looking placebo tablets. The teachers gave the tablets to the children at school at midmorning with water. Pill counts were done at 6, 12, and 20 wk to determine compliance. At baseline, one-half of the children in each group were randomly selected to also receive a single oral dose of 0.4 mL iodized poppy seed oil (Lipiodol, Guerbet, France) containing 200 mg I (13). All children enrolled in the study received a single 400-mg oral dose of albendazole (Zentel; SmithKline Beecham, Uxbridge, United Kingdom) at baseline.

At baseline, 1, 6, 12, and 20 wk, spot urine samples were collected for the measurement of urinary iodine, and dried blood spots were prepared for the measurement of thyrotropin and thyroxine. At baseline, 6, 12, and 20 wk, weight, height, and ultrasonographic thyroid gland volume were measured, and at baseline, 12, and 20 wk, hemoglobin, serum ferritin, TfR, and zinc protoporphyrin were measured. Salt samples were collected from random households (n = 45) of both groups of children at 1, 12, and 20 wk. On completion of the study, the children who had received placebo and remained anemic were treated with iron.

Laboratory analyses

Serum and urine samples were portioned and frozen at −20°C until analyzed. Urinary iodine was measured by using a modification of the Sandell-Kolthoff reaction (14). Salt iodine content was measured by titration with sodium thiosulfate (15). Dried blood spots on filter paper were analyzed for whole-blood thyrotropin and serum thyroxine by immunnasay (16). Hemoglobin was measured with an AEL8 Counter (Beckman Coulter, Krefeld, Germany). Zinc protoporphyrin was measured in washed red blood cells with a hematofluorometer (Aviv Biomedical, Lakewood, NJ). Serum ferritin and TfR were measured by enzyme-linked immunosorbent assay (17, 18). Iron deficiency was defined with the use of multiple criteria (19): serum ferritin < 15 µg/L, TfR > 8.5 mg/L + zinc protoporphyrin > 40 µmol/mol heme, or TfR:serum ferritin > 500 (18). Anemia was defined as hemoglobin < 120 g/L in children aged ≥12 y and hemoglobin < 115 g/L in children aged 5–11 y (20). Thyroid gland volume was calculated by the method of Brunn et al (21). SYH or MBZ performed the ultrasound measurements during the screening, and SYH performed all ultrasound measurements during the intervention. To estimate intra- and interobserver variability, SYH measured 20 children twice and MBZ measured the same children once. The mean (±SD) intra- and interobserver errors were 4.9 ± 4.0% and 3.7 ± 3.5%, respectively. Because current World Health Organization/International Council for the Control of Iodine Deficiency Disorders (WHO/ICCIDD) normative values for thyroid gland volume are being revised (12), we used previous ICCIDD references for school-aged children according to sex and age to define the presence of absence of goiter (22).

Statistical analyses

Data processing and statistics were done with the use of SPLUS 2000 (Mathsoft, Seattle), PRISM3 (GraphPad, San Diego), and EXCEL 97 (Microsoft, Seattle). Normally distributed data were expressed as means (±SDs) and were compared by Student’s t test. Variables not normally distributed were expressed as medians and ranges and were compared by Wilcoxon and Mann-Whitney tests. A two-factor repeated-measures analysis of variance was done to compare the effects of time and group and time × group interaction for hemoglobin, indexes of iron status, urinary iodine, thyrotropin, thyroxine, thyroid gland volume, and percentage change in thyroid gland volume. If the interaction effect was significant, individual means were compared by using t tests between groups and paired t tests within groups, with adjustment for multiple comparisons (Bonferroni’s correction). Proportions were compared by using the chi-square test. In addition, logistic regression was done to compare the effects of time and group and time × group interaction for the binary variables of goiter, anemia, and iron deficiency. Multiple regression was used to test for associations. Significance was set at P < 0.05.

RESULTS

The results of the screening study are shown in Table 1. The median urinary iodine concentration was 162 µg/L. Only 1% and 3% of the children had a urinary iodine concentration < 20 or < 50 µg/L, respectively. The mean (±SD) salt iodine content was 25.2 ± 18 µg/g. Despite adequate urinary and salt iodine concentrations, the prevalence of goiter by ultrasound was 58.6%. The median thyrotropin and the mean serum thyroxine concentrations were within the normal reference range; only 3% of the children had an elevated thyrotropin value and only 1% had a low serum thyroxine value. The prevalence of iron deficiency was 38% and 224 children (23%) were both goitrous and iron deficient.
<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of the children at screening1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Value</td>
</tr>
<tr>
<td>Age (y)</td>
<td>8.9 ± 2.5 (4–16)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.2 ± 1.5</td>
</tr>
<tr>
<td>No. of subjects with goiter [n (%)]</td>
<td>594 (59)</td>
</tr>
<tr>
<td>Urinary iodine (µg/L)2</td>
<td>162 (16–1017)</td>
</tr>
<tr>
<td>Whole-blood thyrotropin (mIU/L)3</td>
<td>0.7 (0.2–4.4)</td>
</tr>
<tr>
<td>Serum thyroxine (nmol/L)4</td>
<td>126 ± 29</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>120 ± 13</td>
</tr>
<tr>
<td>No. of subjects with iron deficiency [n (%)]</td>
<td>364 (38)</td>
</tr>
<tr>
<td>No. of subjects with iron deficiency anemia [n (%)]</td>
<td>178 (19)</td>
</tr>
<tr>
<td>No. of subjects with iron deficiency + goiter [n (%)]</td>
<td>224 (23)</td>
</tr>
</tbody>
</table>

1 n = 698 boys, 316 girls. 
2 ± SD; range in parentheses. 
3 Measured in 400 randomly selected children. 
4 Median; range in parentheses. 
5 Measured in 160 randomly selected children. 

Characteristics of the iron-treated and placebo groups at baseline are compared in Table 2. There were no significant differences at baseline between groups. Of the 169 children who began the study, 166 completed it. Three children moved away and could not be located (all in the placebo group). Pill counts estimated compliance to be >90% in both the iron-treated and placebo groups. The median urinary iodine concentrations (and ranges) in the salt samples from random households in the iron-treated and placebo groups at 1, 12, and 20 wk were 20.1 (4.3–86.6), 16.1 (9.5–40.2), and 12.8 (7.6–67.3) µg/L, respectively. Within both the iron-treated and placebo groups, comparing the subgroups of children who received the additional iodized oil with those who consumed only iodized salt, we found no significant differences in hemoglobin, iron-status indicators, thyrotropin, thyroxine, percentage change in thyroid volume from baseline, or goiter prevalence at 6, 12, or 20 wk (data not shown). Therefore, we combined the subgroups and compared the iron+iodine with the placebo+iodine groups in the final analyses.

As shown in Table 3, iron treatment significantly increased mean hemoglobin concentrations. Additionally, the prevalences of iron deficiency and anemia were significantly lower in the iron-treated group than in the placebo group. At 20 wk, iron-status indexes in the iron-treated and placebo groups, respectively, were as follows: mean zinc protoporphyrin, 59 ± 26 and 70 ± 52 µmol/mol heme (P < 0.05); mean serum ferritin, 80.2 ± 39.6 and 67.1 ± 38.3 µg/L (P < 0.05); mean TIR, 10.4 ± 5.3 and 10.7 ± 3.5 mg/L (NS); and mean TR:serum ferritin, 183 ± 172 and 452 ± 527 (P < 0.05). Iron treatment had no measurable effect on growth; there were no significant differences in weight, height, or BMI between the iron-treated and placebo groups at 0, 6, 12, or 20 wk.

Changes in thyroid gland volume and goiter prevalence in the iron-treated and placebo groups are shown in Table 4. At 20 wk, thyroid gland volume was significantly lower in the iron-treated group than in the placebo group. At 20 wk, the mean percentage change in thyroid gland volume in the iron-treated and placebo groups was −22.8 ± 10.7% and −12.7 ± 10.1%, respectively. Although there was no significant difference in the number of subjects with goiter between groups at 6 and 12 wk, at 20 wk the goiter rate was significantly lower in the iron-treated group than in the placebo group. Moreover, as modeled by logistic regression, the probability of goiter was significantly lower in the iron-treated group, and the group difference increased with time (P < 0.02 comparing time and group model relative to time only model).

Thyrotropin, thyroxine, and urinary iodine concentrations of the iron-treated and placebo groups over the 20 wk of follow-up are shown in Table 5. Median thyrotropin and mean serum thyroxine remained within the normal range in both groups throughout the study and there were no significant differences between groups or with baseline at 6, 12, and 20 wk. The median urinary iodine concentrations throughout the study in the children consuming iodized salt alone were well above the WHO/ICCIDD cutoff (100 µg/L) for risk of iodine deficiency (1). In the groups who received the additional dose of oral iodized oil, urinary iodine was significantly higher at 1, 6, 12, and 20 wk than in the groups who received iodized salt alone.
TABLE 4
Change in thyroid volume and goiter prevalence in the children in the iron-treated (n = 85) and placebo (n = 81) groups

<table>
<thead>
<tr>
<th>Time and group</th>
<th>Thyroid volume(a)</th>
<th>Change from baseline</th>
<th>No. of subjects with goiter(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mL)</td>
<td>(%)</td>
<td>(n\ genocide)</td>
</tr>
<tr>
<td>0 wk (baseline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron-treated</td>
<td>5.6 (3.5–16.4)(c)</td>
<td>—</td>
<td>58 (68)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.8 (3.4–24.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron-treated</td>
<td>5.6 (2.9–15.4)(c)</td>
<td>—0.9 ± 13.4(c)</td>
<td>58 (68)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.8 (2.9–22.5)</td>
<td>3.4 ± 13.5</td>
<td>64 (78)</td>
</tr>
<tr>
<td>12 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron-treated</td>
<td>4.9 (2.5–16.0)(c)</td>
<td>—13.2 ± 11.6</td>
<td>46 (54)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.2 (2.4–22.7)</td>
<td>—7.9 ± 11.1</td>
<td>51 (63)</td>
</tr>
<tr>
<td>20 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron-treated</td>
<td>4.3 (2.1–12.9)(c)(d)</td>
<td>—22.8 ± 10.7(c)(d)</td>
<td>37 (43)(d)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.1 (2.1–21.4)(d)</td>
<td>—12.7 ± 10.1</td>
<td>50 (62)</td>
</tr>
</tbody>
</table>

\(a\) To reduce the effects of variability among individuals, change from baseline was calculated for each child before deriving means.

\(\text{Significant treatment } \times \text{time interaction, } P < 0.01 (\text{ANOVA}).\)

\(\text{Prevalence significantly lower in the iron group, } P < 0.02 (\text{comparing time and group model relative to time only model in the logistic regression}).\)

\(\text{Median; range in parentheses.}\)

\(\text{Significantly different from baseline of iron-treated group (paired } t\text{-test); } P < 0.05, 6 P < 0.01.\)

\(\text{Significantly different from baseline of placebo group (paired } t\text{-test); } 6 P < 0.05, 7 P < 0.01, 8 P < 0.01.\)

\(\text{Significantly different from placebo at } 20 \text{ wk } (t\text{-test); } 7 P < 0.01, 8 P < 0.01.\)

\(\text{Significantly different from placebo at } 20 \text{ wk } (\text{chi-square test}).\)

\(\text{Significantly different from baseline of placebo group, } P < 0.05 (\text{paired } t\text{-test}).\)

Multiple regression analysis of percentage change in thyroid gland volume at 20 wk on group, baseline characteristics (in Table 2), and change in hemoglobin from baseline to 20 wk was done. The regression of percentage change in thyroid gland volume at 20 wk on group was significant \((P < 0.0001)\). There was also a significant effect (beyond group) of height, weight, BMI, baseline hemoglobin, change in hemoglobin, and baseline thyroid gland volume. Regression applied to bootstrapped data consistently selected group, baseline height, baseline thyroid gland volume, baseline hemoglobin, and change in hemoglobin as significant predictors for percentage change in thyroid gland volume \((\text{multiple } R^2 = 0.27, P < 0.0001);\) that is, children with larger thyroids at baseline had greater percentage changes in thyroid gland volume, whereas taller children, more severely anemic children, and those with a poorer response to iron treatment had a smaller percentage change in thyroid gland volume.

DISCUSSION

In this study, iron supplementation improved the efficacy of iodized salt and oral iodized oil in goiterous children with iron deficiency. However, the mechanism by which iron deficiency influences the response to iodine in children with IDD is unclear.

Iron deficiency impairs thyroid metabolism in animal and human studies \((6–9)\). In rats, iron deficiency anemia lowers plasma thyroid hormone concentrations, reduces the activity of hepatic thyroxine deiodinase, impairs the peripheral conversion of thyroxine to triiodothyronine, and blunts the thyrotropin response to thyrotropin-releasing hormone \((6, 7)\). Iron-deficient adults have lower circulating concentrations of thyroxine and triiodothyronine \((8, 9)\) and higher concentrations of thyrotropin \((8)\) than do healthy control subjects. Iron deficiency may influence IDD through alterations in the central nervous system control of thyroid metabolism \((6)\) or through modifications in nuclear triiodothyronine binding \((7)\). Also, the initial steps of thyroid hormone synthesis—iodide incorporation into tyrosine residues of thyroglobulin and covalent bridging of the residues—are catalyzed by heme-containing thyeroxidases. Other iron-containing enzymes \([\text{eg, cytochrome oxidase, myeloperoxidase, and succinate dehydrogenase (ubiquinone)}]\) are sensitive to iron deficiency \((23)\). Theoretically, severe iron deficiency could lower thyroxoperoxidase activity and interfere with thyroid hormone synthesis.

In the present study, we gave one-half of the children in both the iron-treated and placebo groups a single 200-mg dose of oral iodide \((13)\) in addition to their daily iodine intake from salt. We were concerned about potential fluctuations in iodine intake from iodized salt alone in a region where transportation, food supply, and infrastructure are precarious. The iodized oil was given to ensure that at least one-half of the children would have an ample and steady supply of iodine during the study period. In hindsight, this was unnecessary. Median urinary iodine remained adequate \((>100 \mu g/L)\) \((1)\) throughout the study in the children consuming only iodized salt. The additional iodine given as iodized oil increased urinary iodine concentrations significantly but otherwise had no discernible effect. Within both the iron-treated and placebo groups, we found no significant differences in thyrotropin, thyroxine, percentage change in thyroid gland volume, or goiter rate at 6, 12, and 20 wk between children who received iodized oil and those who consumed only iodized salt.

The high prevalence of malaria and gastrointestinal infections in children in rural Côte d’Ivoire both contributes to and complicates the diagnosis of iron deficiency in this population \((24)\). Therefore, we used multiple iron-status indicators \((\text{serum ferritin, TFR, and zinc protoporphyrin})\) to confirm iron deficiency at baseline and to monitor the response to iron supplementation \((19)\). Because we wished to investigate the influence of iron status and not anemia per se on response to iodine, we included both iron-deficient and iron-deficient anemic children in the study. By regression analysis, baseline hemoglobin concentrations correlated negatively with percentage change in thyroid gland volume in both the iron-treated and placebo groups, whereas improvement in hemoglobin from baseline to 20 wk was positively associated with percentage change in thyroid gland volume. This suggests that iodine was less efficacious in children with more severe anemia at baseline and in those with a poorer response to iron. In a previous study, we also found a strong correlation between the severity of iron deficiency anemia and percentage change in thyroid gland volume after the oral administration of iodized oil \((10)\).

The high prevalence of malaria and other infections also blunts the response to iron repletion in anemic African children \((25)\). In the present study, response to iron was clearly evident only after 16 wk of supplementation. Moreover, reductions in thyroid size lag behind improvements in thyroid function during the introduction of iodized salt in an area of endemic goiter \((26)\). For these reasons, the effect of iron treatment on thyroid size may...
have been greater if the follow-up had been longer. We did not extend the study past 20 wk because we wanted to limit the delay in iron treatment of the iron-deficient children in the placebo group (27).

The significant improvement in iron status in the placebo group compared with baseline (Table 3) was likely due to several factors. First, we explained to the parents that the children were enrolled in the study because they were sick as a result of poor nutrition. This may have precipitated a change in feeding patterns at home; for example, the children may have received a greater share of the small amounts of meat available at meal times. Second, the availability of mango and pineapple increases during the spring months in rural Côte d’Ivoire; thus, it is possible that intakes of ascorbic acid [a potent enhancer of iron absorption (28)] increased over the course of the study. Third, all of the children were dewormed at the beginning of the study.

This is likely to have reduced iron losses from hookworm and other parasitic infections endemic to this region and may have contributed to the improvement in iron status (25).

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 (29) and that 50% of this anemia is due to iron deficiency, not only to combat anemia but also to increase the efficacy of iodine prophylaxis.
We thank the participating children and the teachers, JB Gbato (Public Health, Côte d’Ivoire), L Molinari (Children’s Hospital, Zürich, Switzerland) for statistical assistance, and Carol Flowers (University of Kansas Medical Center, Kansas City, KS) for assistance with the laboratory analyses.

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