

Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in Côte d'Ivoire¹⁻³

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ABSTRACT

Background: In developing countries, many children are at high risk of goiter and iron deficiency anemia. Because iron deficiency can have adverse effects on thyroid metabolism, iron deficiency may influence the response to supplemental iodine in areas of endemic goiter.

Objective: The aim of this study was to determine whether goitrous children with iron deficiency anemia would respond to oral iodine supplementation.

Design: A trial of oral iodine supplementation was carried out in an area of endemic goiter in western Côte d'Ivoire in goitrous children ($n = 109$) aged 6–12 y. Group 1 ($n = 53$) consisted of goitrous children who were not anemic. Group 2 ($n = 56$) consisted of goitrous children who had iron deficiency anemia. At baseline, thyroid gland volume and urinary iodine, thyrotropin, and thyroxine were measured by using ultrasound. Each child received 200 mg I orally and was observed for 30 wk, during which urinary iodine, thyrotropin, thyroxine, hemoglobin, and thyroid gland volume were measured.

Results: The prevalence of goiter at 30 wk was 12% in group 1 and 64% in group 2. The mean percentage change from baseline in thyroid volume 30 wk after administration of oral iodine was -45.1% in group 1 and -21.8% in group 2 ($P < 0.001$). Among the anemic children, there was a strong correlation between the percentage decrease in thyroid volume and hemoglobin concentration ($r^2 = 0.65$).

Conclusion: The therapeutic response to oral iodine was impaired in goitrous children with iron deficiency anemia, suggesting that the presence of iron deficiency anemia in children limits the effectiveness of iodine intervention programs. *Am J Clin Nutr* 2000;71:88–93.

KEY WORDS Iodine, iron, iron deficiency anemia, goiter, interaction, iodized oil, 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). Iodine deficiency in childhood also impairs neuro-motor and intellectual development, with an average reduction in the intelligence quotient of 10 points (2). There are large areas in western and central Africa where IDDs are endemic; it

is estimated that 250 million people are at risk of IDDs and 50 million have goiter (3). A goal of the World Health Organization (WHO) is global elimination of IDDs by the year 2000 through iodine supplementation (1).

Multiple nutritional and environmental influences contribute to the prevalence and severity of IDDs in iodine-deficient areas (4). General malnutrition, water-borne goitrogens, and a variety of goitrogenic foods can aggravate goiter (5, 6). Deficiencies of selenium (7, 8) and vitamin A (9) may modify thyroid hormone metabolism and potentially exacerbate IDDs.

Another micronutrient that could potentially influence IDDs is iron (10). The 2 initial steps of thyroid hormone synthesis are catalyzed by thyroperoxidases and are dependent on iron. Animal and human studies suggest that iron deficiency impairs thyroid metabolism (11–14). Iron deficiency anemia decreases plasma thyroxine (T_4) and triiodothyronine (T_3) concentrations, reduces peripheral conversion of T_4 to T_3 , and may increase concentrations of thyrotropin (11–14).

Deficiencies of iron and iodine are major public health problems in West Africa, where many children are at high risk of both goiter and iron deficiency anemia (15). In Côte d'Ivoire, more than half of school-age children in the western and northern regions are iodine deficient and 23–25% have iron deficiency anemia (16, 17). The aims of this study were to investigate the relation between iron and iodine deficiencies and, more specifically, to determine whether iodine-deficient, goitrous children with iron deficiency anemia could synthesize thyroid hormones and achieve a reduction in the size of their goiters when given iodine.

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SUBJECTS AND METHODS

Subjects

The study was carried out in 2 isolated villages (Gbanleu and Douangopleu; total population, 1450) in an area of endemic goiter in the Danané health district (17), a mountainous region in western Côte d'Ivoire. The villages are 5 km apart and are similar ethnically. The staple foods in the villages are rice and cassava. The study was approved by the Ethical Review Board of the University Hospital of Zürich, the National Institute of Public Health, and the Ministry of Research of Côte d'Ivoire. Informed consent was obtained from the chiefs of the 2 villages and from the families of the individual children.

Screening population

All children aged 6–15 y in the 2 villages ($n = 419$) were screened. Weight and height were measured and goiter was graded by using WHO criteria (1). Spot urine samples were collected for measurement of urinary iodine. Blood was collected by venipuncture for determination of hemoglobin, whole-blood zinc protoporphyrin (ZnPP), serum ferritin, and serum transferrin receptor (TfR). Blood was spotted onto filter paper for measurement of whole-blood thyrotropin and serum T_4 .

All goitrous children aged 6–12 y with a hemoglobin concentration >120 g/L (group 1) or with iron deficiency anemia (group 2) were then invited to join the intervention study. Iron deficiency anemia was considered to be present if the hemoglobin concentration was <110 g/L and serum ferritin was <12 $\mu\text{g/L}$, or if the hemoglobin concentration was <110 g/L, serum TfR was >8.5 mg/L, and ZnPP was >40 $\mu\text{mol/mol}$ heme (18). Fifty-eight children met the criteria for inclusion in group 1 and 53 were enrolled; 71 children met the criteria for inclusion in group 2 and 56 were enrolled. The remaining children either could not be located or declined to join the study. The investigators were blinded to the group assignment of the children throughout the entire study.

Baseline measurements

On the morning before administration of the iodized oil, all children underwent baseline measurements of iodine in spot urine samples, of thyrotropin and serum T_4 in blood spotted onto filter paper, and of serum retinol and selenium. Thyroid gland volume was measured by using an SSD-500 echocamera (Aloka, Mure, Japan) with a high-resolution 7.5-MHz linear transducer (19).

Methods

Each child in groups 1 and 2 then received an oral dose of 0.4 mL iodized poppy-seed oil (Lipiodol, Guerbet, France) containing 200 mg I. At 1, 5, 10, 15, and 30 wk postintervention, spot urine samples were collected for measurement of urinary iodine and dried blood spots were collected for determination of whole-blood thyrotropin and T_4 . At 10, 15, and 30 wk, thyroid volume was measured by using ultrasound. To avoid interobserver variability, all ultrasound measurements were performed by a single investigator (MZ). At 10, 15, and 30 wk, height and weight were remeasured so that the potential effect of growth on thyroid volume could be accounted for. At 15 wk, spot urine samples were collected for measurement of urinary thiocyanate. At 30 wk, a venous blood sample was collected for redetermination of hemoglobin concentration.

Of the 109 children enrolled in the study, 104 completed it. Of the 5 children who did not complete the study, 1 child in group 1

and 2 children in group 2 had moved away from the area and could not be found. One child in group 1 developed anemia during the study and one child in group 2 was no longer anemic at 30 wk; both of these children were excluded from the final comparisons. The children in group 2 were provided with supplemental iron on completion of the study.

In countries with a high prevalence of child growth retardation, thyroid volume is considered to be more directly a function of total body surface area than of age (20). Therefore, body surface area was calculated from weight and height measurements taken with each ultrasound measurement, and normative values for thyroid volume in children aged 6–12 y according to sex, age, and body surface area were used to define the presence or absence of goiter (20).

Biochemical analyses

Portions of blood and urine samples were frozen at -20°C until analyzed. Urinary iodine was measured by using a modification of the Sandell-Kolthoff reaction (21). Hemoglobin was measured by using the cyanmethemoglobin method with kits (Sigma Diagnostics, St Louis) and 3-level quality-control materials (DiaMed, Cressier sur Morat, Switzerland). The hemoglobin values used in the correlations were the means of the 2 hemoglobin measurements (baseline and 30 wk). ZnPP was measured in washed red blood cells by using a hematofluorometer (Aviv Biomedical, Lakewood, NJ). Serum ferritin and TfR were measured by using commercial kits (RAMCO, Houston). Urinary thiocyanate was analyzed by a colorimetric method (22). Serum retinol was measured by HPLC (23). Serum selenium was measured by atomic absorption spectrometry with the Zeeman background correction (model 4100 ZL; Perkin-Elmer, Norwalk, CT) (24) with a limit of sensitivity of 6.5 $\mu\text{g/L}$; undetectable concentrations were assigned a value of 6.5 $\mu\text{g Se/L}$. Dried blood spots on filter paper were analyzed for whole-blood thyrotropin and serum T_4 by immunoassay (25). Because normal hemoglobin values may be lower in black persons, a WHO-1 cutoff was used for anemia to ensure that the iron-deficient children in this study were anemic (26). Normal reference values are as follows: urinary iodine, 50–250 $\mu\text{g/L}$; ratio of urinary iodine to thiocyanate (UI:SCN), >3 $\mu\text{g/mg}$ (27); serum sele-

TABLE 1
Characteristics of children at screening¹

Characteristic	Value
Age (y)	8.8 \pm 2.7 ² (6–15) ³
Sex (% male)	55
BMI (kg/m ²)	16.4 \pm 2.2
No. of subjects with grade 1 goiter	178 [42.4]
No. of subjects with grade 2 goiter	10 [2.4]
Urinary iodine ($\mu\text{g/L}$)	28 (36, 43) ⁴
No. of subjects with <2 $\mu\text{g/L}$	116 [27.6]
No. of subjects with <5 $\mu\text{g/L}$	336 [80.1]
No. of subjects with <10 $\mu\text{g/L}$	386 [92.1]
Whole-blood thyrotropin (mU/L)	0.8 (0.8, 1.3) ⁴
Serum thyroxine (nmol/L)	137 \pm 36
Hemoglobin (g/L)	111 \pm 15
No. of subjects with anemia (hemoglobin <110 g/L)	209 [49.8]
No. of subjects with iron deficiency anemia	115 [27.4]
No. of subjects with goiter and iron deficiency anemia	78 [18.6]

¹ Percentages in brackets.

² $\bar{x} \pm$ SD.

³ Range.

⁴ Median; 95% CI in parentheses.

TABLE 2

Baseline characteristics of goitrous children with (group 2) and without (group 1) anemia

Characteristic	Group 1 (n = 28 M, 23 F)	Group 2 (n = 27 M, 26 F)
Age (y)	8.6 ± 1.9 ¹	8.2 ± 1.9
Weight (kg)	25.9 ± 6.2	23.1 ± 6.4 ²
Height (cm)	128 ± 13	120 ± 14 ²
BMI (kg/m ²)	15.8 ± 1.5	15.9 ± 1.7
Hemoglobin (g/L)	125 ± 4	97 ± 8
Serum ferritin (μg/L)	77.2 ± 31	16.1 ± 5.9
Serum transferrin receptor (mg/L)	6.6 ± 4.1	122.6 ± 31.4
Whole-blood zinc protoporphyrin (μmol/mol heme)	23 ± 12	71 ± 26
Urinary iodine (μg/L)	29 (30, 47) ³	27 (28, 46)
Whole-blood thyrotropin (mU/L)	1.1 (1.1, 1.3)	0.8 (0.8, 1.4)
Serum thyroxine (nmol/L)	111 ± 23	130 ± 28 ⁴
Thyroid volume (mL)	8.5 ± 2.0	8.1 ± 1.9
Serum retinol (μmol/L)	0.65 ± 0.39	0.66 ± 0.43
Urinary iodine–thiocyanate ratio (μg/mg)	1.9 (1.9, 3.5)	1.7 (1.7, 4.3)
Serum selenium (μg/L)	14.4 ± 7.8	16.4 ± 9.3

¹ $\bar{x} \pm SD$.²Significantly different from group 1, $P < 0.05$.³Median; 95% CI in parentheses.⁴Significantly different from group 1, $P < 0.01$.

nium, 65–105 μg/L; serum retinol, 0.35–1.75 μmol/L; serum ferritin, 12–300 μg/L; TfR, 2.9–8.5 mg/L; ZnPP, <40 μmol/mol heme; whole-blood thyrotropin, <3.5 mU/L; and serum T₄, 65–165 nmol/L.

Statistics

Normally distributed data were expressed as means ± SDs and were compared by using Student's *t* test. Variables that were not normally distributed (urinary iodine, thyrotropin, and UI:SCN) were expressed as medians with 95% CIs and were compared by using the Wilcoxon signed-rank test and the Mann-Whitney *U* test. A two-factor repeated-measures analysis of variance was done to compare effects of time and group and time by group for urinary iodine, thyrotropin, T₄, and the percentage change in thyroid volume after intervention. Multiple regression was used to test for associations. Statistical analyses were done by using PRISM (Graphpad, San Diego) and SAS (SAS Institute, Inc, Cary, NC).

RESULTS

Screening population

The results of the screening are shown in **Table 1**. The median urinary iodine concentration was 28 μg/L, and 27.6% and 80.1% of the children had a urinary iodine concentration <20 and <50 μg/L, respectively. The prevalence of goiter was 45%, and 95% of these goiters were grade 1. The median thyrotropin concentration and the mean serum T₄ concentration were both within the normal reference range; only 1% of the children had an elevated thyrotropin value and 2% had a low serum T₄ concentration. Half of the children were anemic (hemoglobin concentration <110 g/L) and 55% of the anemia was due to iron deficiency (18). Nearly 20% of the children were both goitrous and anemic with iron deficiency.

Study population

Comparisons between groups 1 and 2 at baseline are shown in **Table 2**. There were no significant age or sex differences

between the groups. Although the body mass indexes of the groups were not significantly different, the mean height and weight in group 2 were significantly less than in group 1. Overall, the children in group 2 were moderately anemic (mean hemoglobin = 97 g/L); 20% of the children had hemoglobin concentrations <90 g/L. There were no significant differences in thyroid volume, whole blood thyrotropin, serum retinol, serum selenium, urinary iodine, or UI:SCN between the groups.

The changes in thyroid volume after administration of the iodized oil in groups 1 and 2 are shown in **Table 3**. Thyroid volume decreased significantly compared with baseline in both groups at 10 wk. At 15 and 30 wk there was no further decrease in group 2, whereas in group 1 thyroid volume continued to fall. At 15 and 30 wk, thyroid volume was significantly lower in group 1 than in group 2. At 30 wk the mean percentage change in thyroid volume from baseline was –45% in group 1 and –22% in group 2. These differences were reflected in the change in the prevalence of goiter at 10, 15, and 30 wk (**Figure 1**). A sharp difference in prevalence was apparent at 15 and 30 wk, when the percentages of children with goiter were 62% and 64%, respectively, in group 2 but only 31% and 12%, respectively, in group 1.

The changes in thyrotropin, T₄, and urinary iodine in groups 1 and 2 over the 30 wk of follow-up are shown in **Table 4**. Urinary iodine was significantly higher than that at baseline at 30 wk in both groups; the medians at 30 wk were 150–160 μg/L, still well above the WHO cutoff value for risk of IDD (100 μg/L) (1). Although median thyrotropin and mean serum T₄ at baseline and at follow-up were within the normal range in both groups, mean serum T₄ at baseline was significantly greater in group 2 than in group 1. In group 2 at 1 wk, there was no significant change from baseline in mean serum T₄ but there was a significant transient rise from baseline in the median thyrotropin value, consistent with a mild Wolff-Chaikoff effect. Median thyrotropin values at 5, 10, 15, and 30 wk were significantly lower than those at baseline in group 1. At 15 and 30 wk, median thyrotropin values were significantly lower in group 1 than in group 2. Mean serum T₄ increased significantly from baseline in group 1 at 30 wk and was significantly greater in group 1 than in group 2 at 15 and 30 wk. These values suggest that thyroid hormone status improved after treatment with iodized oil in group 1 but not in group 2.

TABLE 3Changes in thyroid volume in goitrous children with (group 2) and without (group 1) anemia 10, 15, and 30 wk after receipt of 200 mg oral I¹

Thyroid volume	Group 1 (n = 51)	Group 2 (n = 53)
Baseline (mL)	8.5 ± 2.0	8.1 ± 1.9
10 wk (mL)	6.5 ± 1.7 ²	6.5 ± 2.6 ²
Change from baseline (%)	–22.3 ± 17.3	–20 ± 19.5
15 wk (mL)	5.1 ± 1.5 ^{2,3}	6.3 ± 2.4 ²
Change from baseline (%)	–30.7 ± 14.8	–22.8 ± 18.8
30 wk (mL)	4.6 ± 1.5 ^{2,3}	6.3 ± 2.1 ²
Change from baseline (%)	–45.5 ± 12.0	–21.8 ± 17.2

¹ $\bar{x} \pm SD$. To reduce the effects of variability among individuals, the percentage change from baseline was calculated for each child before the means were derived.

²Significantly different from baseline, $P < 0.001$.³Significantly different from group 2, $P < 0.001$.

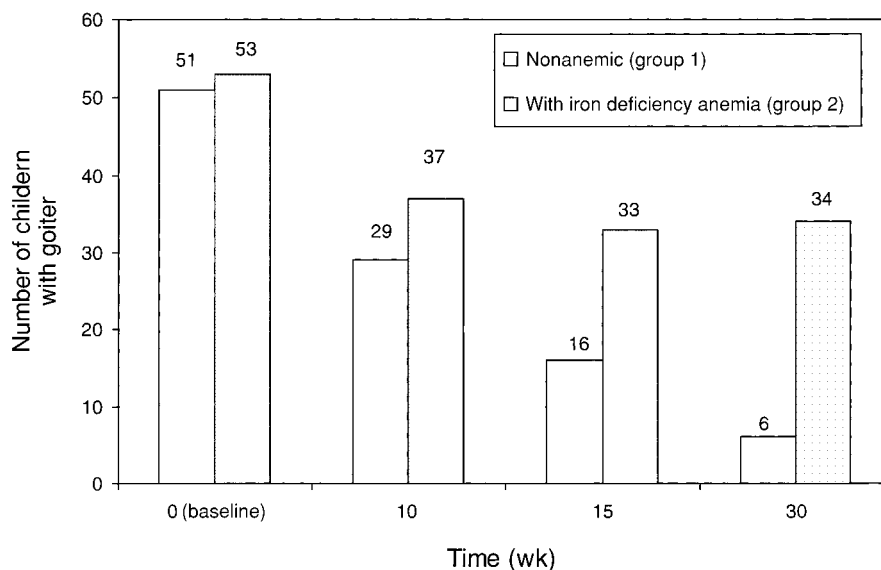


FIGURE 1. Number of children in group 1 ($n = 53$) and group 2 ($n = 56$) with goiter 10, 15, and 30 wk after oral administration of 200 mg I, as assessed by ultrasound.

To test for associations, multiple regression of the percentage change in thyroid volume at 30 wk was done for hemoglobin, serum retinol, serum selenium, and UI:SCN. The regression of percentage change in thyroid volume on hemoglobin was highly significant ($P < 0.001$). The addition of serum retinol, serum selenium, or UI:SCN to the analysis did not improve the prediction. The strong correlation ($r^2 = 0.606$) between hemoglobin and the percentage change in thyroid volume is shown in **Figure 2**.

DISCUSSION

Although deficiencies of iron and iodine are major overlapping public health concerns in developing countries, previous studies of the relation between iron deficiency and goiter are limited. A survey of Ethiopian children showed no correlation between iron status and goiter rate or thyroid hormone concentrations (9). There were no significant differences in the

prevalence of goiter in anemic and nonanemic children and adults in a survey in the Philippines (28). In Ethiopian children who were severely vitamin A deficient, low T_3 concentrations were associated with low serum iron and low transferrin saturation (29).

Studies in animals and humans showed that iron deficiency impairs thyroid metabolism. In rats, iron deficiency reduces plasma thyroid hormone concentrations, reduces the activity of hepatic thyroxine deiodinase, impairs peripheral conversion of T_4 to T_3 , and blunts the thyrotropin response to thyrotropin-releasing hormone (12, 30). Compared with healthy control subjects, iron-deficient adults have lower circulating T_4 and T_3 concentrations (11, 13, 14) and higher thyrotropin concentrations (14). Although the mechanism for these effects is unclear, 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 thyroperoxidases. Other iron-containing enzymes (eg, cytochrome-*c* oxidase, myeloperoxidase, and succi-

TABLE 4

Changes in whole-blood thyrotropin, serum thyroxine (T_4), and urinary iodine in goitrous children with (group 2) and without (group 1) anemia after receipt of 200 mg oral I

Time after iodine administration	Thyrotropin ¹		T_4 ²		Urinary iodine ¹	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
	mU/L		nmol/L		μg/L	
0 wk (baseline)	1.1 (1.1, 1.4)	0.8 (0.8, 1.4)	110 ± 22	130 ± 28 ³	29 (30, 47)	27 (28, 46)
1 wk	1.1 (1.1, 1.5)	2.1 (2.0, 2.5) ^{4,5}	113 ± 22	131 ± 27 ³	992 (919, 1500) ⁶	1210 (1450, 2490) ^{3,6}
5 wk	0.6 (0.5, 0.7) ⁶	0.7 (0.7, 1.0)	115 ± 21	100 ± 22	281 (262, 358) ⁶	359 (331, 445) ⁶
10 wk	0.6 (0.5, 0.8) ⁶	0.8 (0.7, 1.0)	110 ± 26	101 ± 25 ⁵	168 (165, 231) ⁶	176 (172, 266) ⁶
15 wk	0.5 (0.4, 0.6) ⁶	0.8 (0.8, 1.0) ³	122 ± 24	96 ± 17 ^{4,5}	181 (165, 218) ⁶	176 (172, 266) ⁶
30 wk	0.6 (0.5, 0.6) ⁶	1.0 (1.1, 1.4) ⁴	156 ± 30 ⁵	123 ± 30 ⁴	125 (115, 143) ⁶	143 (128, 180) ⁶

¹Median; 95% CI in parentheses.

² $\bar{x} \pm$ SD.

^{3,4}Significantly different from group 1: ³ $P < 0.01$, ⁴ $P < 0.001$.

^{5,6}Significantly different from baseline: ⁵ $P < 0.01$, ⁶ $P < 0.001$.

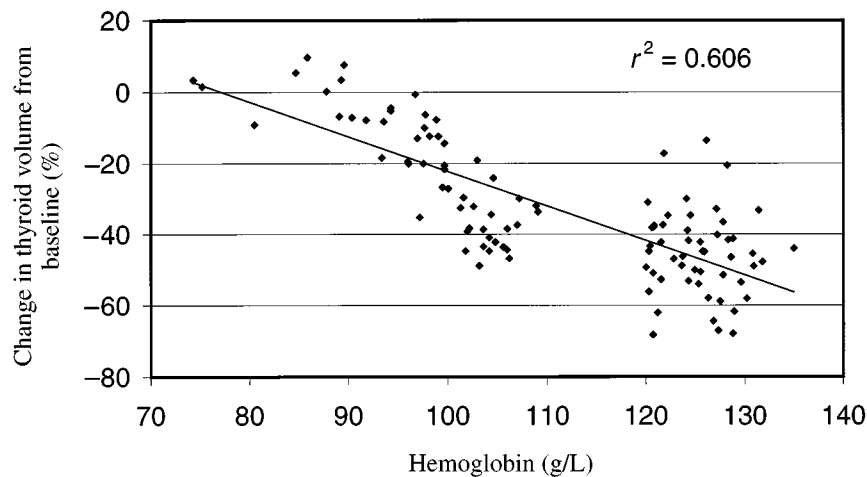


FIGURE 2. Correlation between hemoglobin and the percentage change in thyroid volume from baseline in group 1 (hemoglobin concentration >120 g/L) and group 2 (hemoglobin concentration <110 g/L) at 30 wk.


nate dehydrogenase) are sensitive to depletion of iron (31, 32). Theoretically, severe iron deficiency could lower thyroperoxidase activity and interfere with thyroid hormone synthesis (10).

Iron may be only one of many nutritional and environmental factors that influence the pathogenesis of IDD in iodine-deficient areas. Protein-energy malnutrition (4, 33), food goitrogens (5, 6, 27), and deficiencies of selenium (5–7) and vitamin A (8, 34) may aggravate goiter. However, these factors are unlikely to explain the difference in response to oral iodine between the 2 groups of children in this study. There were no visible signs of protein-energy malnutrition and the mean body mass indexes of the children were similar and near the 50th percentile for black children from the United States (35). Although many of the subjects had low concentrations of selenium and vitamin A in serum, there were no significant differences in the mean concentrations of these micronutrients between the 2 groups. Cassava is one of the staple foods of western Côte d'Ivoire and median UI:SCN ratios were low (<3 $\mu\text{g}/\text{mg}$), indicating increased risk of exacerbation of goiter by thiocyanate (27). However, there were no significant differences in UI:SCN between the groups. Furthermore, when multiple regression was used, serum retinol, serum selenium, and UI:SCN were not significantly correlated with the percentage change in thyroid volume 30 wk after administration of oral iodine, whereas regression of percentage change in thyroid volume on hemoglobin concentration was highly significant.

Iron deficiency in the anemic subjects was confirmed by using multiple iron-status indicators (ferritin, TfR, and ZnPP) at baseline. At 30 wk postintervention, hemoglobin was remeasured in all subjects but, because of technical considerations in the field, we were unable to redetermine iron status. Persistent anemia (hemoglobin < 110 g/L) in subjects who were previously diagnosed with iron deficiency anemia was assumed to be due to continuing iron deficiency. Only one child in group 2 was no longer anemic at 30 wk and was excluded from the final comparisons.

Thyroid ultrasonography is a precise and objective method for measuring goiter size (1, 36) that has become feasible for field studies even in remote areas. In this study, a durable and portable echocamera with a high-resolution transducer was carried into

the field and, in an area without electricity, run with a small generator. Each assessment required only a few minutes per subject. There was a striking reduction in the prevalence of goiter in group 1 at 15 and 30 wk after the iodized oil was ingested. The mean (\pm SD) percentage decrease in thyroid volume from baseline was 45.5% (12.0), and only 12% of the children remained goitrous at 30 wk. This marked reduction in the prevalence of goiter is more pronounced than the reductions found in most previous studies (37–42) but, because of varying conditions in these studies (age of subjects, severity of iodine deficiency, geographic location, whether ultrasound or palpation was used to grade goiters, and follow-up intervals), it is difficult to compare results. In a study of goitrous adults in Zaire, a 118-mg oral dose of iodine reduced thyroid size (as measured by a thyroid-tracing method) by 36% at 3 mo and by 52% at 1 y (43).

The findings in this study suggest that iron deficiency anemia in children may limit the effectiveness of an iodine intervention program. If confirmed, this result will have broad public health implications for the control of IDD. More than 2 billion people—mainly young women and children, most in developing countries—are iron deficient (44). Children and pregnant women are also highly vulnerable to iodine deficiency and are the main target groups for iodine-supplementation programs (1, 3). Of the 419 children screened in this study, nearly 1 in 5 had both goiter and iron deficiency anemia. If iron deficiency is a nutritional factor that influences the pathogenesis of IDD, iron deficiency may have a greater effect on IDD than do previously described goitrogens because of its high prevalence in vulnerable groups. 

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