Thyroid size and goiter prevalence after introduction of iodized salt: a 5-y prospective study in schoolchildren in Côte d'Ivoire[1–3]

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ABSTRACT

Background: The long-term goal of salt iodization is elimination of iodine deficiency and reduction of the goiter rate to < 5% in school-aged children. Normalization of the goiter rate probably indicates disappearance of iodine deficiency disorders as a public health problem. However, thyroid size may not return to normal for months or years after correction of iodine deficiency.

Objective: We described the time course and pattern of changes in thyroid size and goiter rate in response to the introduction of iodized salt in an area of severe endemic goiter.

Design: In a 5-y prospective study, we measured thyroid size by ultrasonography and urinary iodine and thyroid hormone concentrations in schoolchildren 6 mo before the introduction of iodized salt and annually for 4 y thereafter.

Results: Four years after the introduction of iodized salt and normalization of the median urinary iodine concentration, mean thyroid size had decreased 56% ($P < 0.0001$). However, 29% of the children remained goitrous, with a significant age shift in the distribution of goiter. At baseline, the goiter rate was significantly higher in younger (age: 5–9 y) than in older (age: 10–14 y) children ($P < 0.0001$). At 2, 3, and 4 y after salt iodization, the goiter rate was significantly higher in the older than in the younger children (at 4 y: 52% compared with 19%), and the difference increased with time ($P < 0.0001$).

Conclusion: The goiter rate in school-aged children may remain sharply elevated for up to 4 y after successful introduction of iodized salt, primarily because of persistent goiter in older children. *Am J Clin Nutr* 2003;77:663–7.

KEY WORDS Iodine, iron, deficiency, anemia, goiter, thyroid, iodized salt, prospective, children Côte d'Ivoire

INTRODUCTION

The success of universal salt iodization (USI) for the control of the iodine deficiency disorders (IDD) requires monitoring of its effect at a population level. The principal indicator of effect is the median urinary iodine concentration (UI), because it is highly sensitive to recent changes in iodine intake (1). A second indicator is thyroid size, as reflected by the goiter rate (GR). Although thyroid size changes inversely in response to alterations in iodine intake, there is a lag before the GR normalizes after iodine repletion. The duration of this lag period is unclear, with experts suggesting it may last from months to years (2). During this period, the GR is a poor indicator of effect because it reflects a population's history of iodine nutrition but not its present iodine status. Cross-sectional studies have reported a discrepancy between the UI and the GR in the immediate post–USI introduction period (3, 4).

Despite this, the GR, when accurately assessed, remains an important and sensitive long-term indicator of the success of an iodine program. By increasing access to iodized salt and increasing UI, the ultimate goal of USI is normalization of thyroid function in individuals affected by IDD. Because goiter represents maladaptation of the thyroid to iodine deficiency (5, 6), the reduction of the GR to < 5% in school-aged children probably indicates the disappearance of IDD as a significant public health problem (1).

Although large doses of oral or injected iodized oil rapidly reduce the GR (7, 8), many studies used thyroid palpation to grade goiter. Palpation is subjective, and its sensitivity and specificity are low (1). Particularly in areas of mild-to-moderate IDD and for monitoring the effect of USI, measurement of thyroid size by ultrasonography is preferable to palpation (9). Although estimating the GR in children on the basis of thyroid size has been hampered by the difficulty of establishing references for thyroid volume in school-aged children, the World Health Organization (WHO) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) recently published updated reference criteria (10).

In Chinese schoolchildren affected by mild IDD, the GR, as measured by ultrasonography, was reduced from 18% to 5–9% after 18 mo of salt iodization (11). We are aware of no other long-term prospective studies that used ultrasonography to measure changes in thyroid size and the GR after introduction of iodized salt in IDD-affected children. Populations in western Côte d'Ivoire were severely affected by IDD until 1998 (12), when USI was successfully introduced. We therefore conducted a 5-y study of school-aged children in this region, measuring thyroid size, UI, and thyroid hormones before and after the introduction of USI.

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SUBJECTS AND METHODS

The study was done in 6 remote villages in the Danané Health District, a mountainous region of western Côte d'Ivoire. The villages are located within an ≈10-km radius in dense forest and have no electricity or running water. Most families are engaged in small-scale subsistence farming. The staple foods are rice and cassava. During the 5-y study period, the quantity and quality of local harvests were stable. The villages are similar ethnically and socioeconomically. Before the introduction of USI, the GR by palpation in western and northern Côte d'Ivoire was 40–60% (13). The study was approved by the Ethical Review Board of the Children's Hospital of the University of Zürich, the National Institute of Public Health, and the Ministry of Research of Côte d'Ivoire. Informed oral consent was given by the village chiefs, teachers, and parents. In late 1997, Côte d'Ivoire legislated mandatory USI at a production level of 30–50 ppm. In February–March 1998, iodized salt was introduced into the Danané region. By 1999, it was estimated that > 80% of Ivorian households had access to iodized salt at a market level of 20–30 ppm (P Adou, unpublished data, 2000). The present study was done from 1997 through 2001.

The subjects were schoolchildren recruited from 6 primary schools. The study visits were done in the same month (November) in the midst of the dry season for 5 consecutive years. All children aged 5–14 y attending school on days when the fieldwork was done were measured. School attendance is only sporadic in this region, so samples from the 5 y varied in size. Children were recruited from 2 schools in 1997 and 1998 and all 6 schools in 1999–2001. Age and sex were recorded, and weight was measured with a calibrated and leveled digital scale to the nearest 100 g. Height was measured to the nearest millimeter with a metal measuring tape (Kirchner & Wilhelm, Stuttgart, Germany). Spot urine samples were collected for measurement of the UI. Whole blood was spotted onto filter paper for measurement of thyroxine in 1997–1999 and thyrotropin in 1997–2001. In 1999, thyroxine and thyrotropin were measured in 51 children randomly selected from the sample; in other years, all children were measured. In 1997, goiter was graded by either palpation with the use of WHO criteria (n = 291) or thyroid ultrasonography (n = 128) (1). In 1998–2001, thyroid size was measured with an Aloka SSD-500 Echocamera (Mure, Japan) with a high-resolution 7.5-MHz linear transducer, with the subjects sitting and their necks slightly extended. SYH and MBZ performed all the ultrasonography measurements over the 5 y. Each year, salt samples were collected from random households of participating children. In addition, to evaluate potential goitrogenic factors, in 1997 and in 1999 whole blood was collected by venipuncture for determination of hemoglobin, serum ferritin (SF), whole-blood zinc protoporphyrin (ZnPP), serum transferrin receptor (TfR), serum selenium, and serum retinol, and a spot urine sample was collected for measurement of urinary thiocyanate.

Laboratory analyses

Urine and blood samples were transported on ice to the regional hospital laboratory. Serum and urine samples were separated into aliquots and frozen at −20 °C until analysis. The UI was measured with a modification of the Sandell-Kolthoff reaction (14). At UIs of 47 and 79 μg/L, the CVs of this assay in our laboratory are 10.3% and 12.7%, respectively. The iodine concentration in salt was measured by titration with thiosulfate (15). The CV of this measurement in our laboratory is 0.64 at 10 μg/g. Dried blood spots on filter paper were analyzed for whole-blood thyrotropin and serum thyroxine with the use of an immunoassay (16). To convert whole-blood thyrotropin values to serum values, whole-blood thyrotropin values were multiplied by 2. Normal reference values are < 3.5 mU thyrotropin/L and 65–165 nmol thyroxine/L. Hemoglobin was measured with an AcT8 Counter (Beckman Coulter, Krefeld, Germany). ZnPP was measured on washed red blood cells with a hematofluorometer (Aviv Biomedical, Lakewood, NJ). SF and TfR were measured with an enzyme-linked immunosorbent assay (17, 18). Normal reference values are 12–300 μg SF/L, 2.9–8.5 mg TfR/L, and < 40 μmol ZnPP/mol heme.

Iron deficiency was defined by multiple criteria: SF < 15 μg/L or TfR > 8.5 mg/L + ZnPP > 40 μmol/mol heme. Because normal values for hemoglobin may be lower in black persons, a WHO reference cutoff of −10 g/L was used for anemia (19). Thyroid volume was calculated by the method of Brunn et al (20). In countries with a high prevalence of child growth retardation, thyroid volume is considered to be more directly a function of body surface area than of age (1). Therefore, body surface area was calculated from weight and height measurements taken with each ultrasonography measurement. Updated WHO/ICCIDD normative values for thyroid volume in school-aged children according to sex and body surface area were used to define goiter (10). In 1999 and 2001, to estimate intra- and interobserver variability in thyroid ultrasonography, SYH measured 20 children twice and MBZ measured the same children once. The mean (± SD) intra- and interobserver errors were 4.7 ± 3.9% and 3.5 ± 2.5%, respectively. Urinary thiocyanate was analyzed by a colorimetric method (21). Serum selenium was measured by atomic absorption spectrometry with the Zeeman background correction (Model 4100 ZL; Perkin-Elmer, Norwalk, CT; 22), with a limit of sensitivity of 6.5 μg/L; undetectable concentrations were assigned a value of 6.5 μg Se/L. Serum retinol was measured by HPLC (23). Normal reference values are > 3 μg UI/mg thiocyanate (23), > 0.70 μmol serum retinol/L, and 65–105 μg serum Se/L.

Statistical analyses

Data processing and statistical analysis were done with GRAPHPAD PRISM3 (version 3; GraphPad, San Diego) and EXCEL 97 (Microsoft, Seattle). Although follow-up data were not obtained for individual children, the same schools were sampled at yearly visits, so overlap between the samples was considerable. For the data analysis, a conservative approach was taken, and the samples were considered independent. Age, height, weight, salt iodine concentration, UI, thyrotropin, thyroxine, and thyroid volume were compared with the use of one-way ANOVA across years and Tukey's test for post hoc comparisons. Variables not normally distributed (UI, thyrotropin, thyroid volume) were logarithmically transformed before analysis. Proportions were compared with the use of the chi-square test. Logistic regression was done to compare the effects of time and group (older compared with younger children) on the percentage change in thyroid volume from baseline and the GR. Significance was set at $P < 0.05$.

RESULTS

There were no significant differences in the mean age, weight, or height of the children sampled at each visit (**Table 1**). Reflecting the local preference for sending boys to school, 63% of the

TABLE 1
Age, sex, height, weight, serum thyrotropin and thyroxine, urinary iodine, and salt iodine concentrations in 5–14-y-old children in Côte d'Ivoire before and after introduction of iodized salt[1]

	Before iodization	After iodization			
	1997 (n = 419)	1998 (n = 204)	1999 (n = 641)	2000 (n = 507)	2001 (n = 526)
Age (y)[2,3]	8.8 ± 2.7	8.5 ± 2.5	8.9 ± 2.3	8.8 ± 2.3	8.5 ± 2.3
Sex (M:F)	231:188	115:89	441:200	333:174	337:189
Height (m)[2,3]	1.27 ± 0.17	1.24 ± 0.19	1.28 ± 0.13	1.25 ± 0.14	1.25 ± 0.16
Weight (kg)[2,3]	24.9 ± 7.1	25.1 ± 6.7	25.8 ± 7.3	24.8 ± 7.4	24.4 ± 6.9
Serum thyrotropin (mU/L)[4,5]	2.2 (0.4–76.4)[a]	1.2 (0.6–24.6)[b]	1.4 (0.4–8.8)[b]	1.4 (0.4–8.2)[b]	1.4 (0.4–16.2)[b]
No. of subjects with >3.5 mU/L[6]	35 [8][a]	12 [6][a]	1 [2][b]	16 [3][b]	13 [2][b]
Serum thyroxine (nmol/L)[2,3]	137 ± 36	122 ± 25	126 ± 29	Not measured	Not measured
No. of subjects with <65 nmol/L[6]	12 [2]	4 [2]	1 [2]		
Urinary iodine (μg/L)[4,5]	28 (5–176)[a]	86 (12–541)[b]	161 (16–936)[c]	133 (4–1339)[c]	104 (8-785)[b]
No. of subjects <20	117 [28]	16 [8]	3 [1]	14 [3]	12 [2]
No. of subjects <50	337 [80]	31 [15]	5 [2]	66 [13]	59 [11]
No. of subjects <100	392 [94]	106 [52]	45 [21]	188 [37]	276 [52]
Salt iodine (μg/g)[7]	<2 [52][a]	11 ± 9 [23][b]	25 ± 18 [213][c]	16 ± 5 [58][d]	11 ± 5 [94][b]

[1] Percentage in brackets. Values in the same row with different superscript letters are significantly different, $P < 0.05$. Significance of post hoc comparisons is given in the text.
[2] Compared by using one-way ANOVA across years (NS).
[3] $\bar{x}$ ± SD.
[4] Compared by using one-way ANOVA on logarithmically transformed data across years ($P < 0.0001$). Tukey's test for post hoc comparisons.
[5] Median; range in parentheses.
[6] Compared by using chi-square test.
[7] n in brackets. Compared by using one-way ANOVA across years ($P < 0.0001$). Tukey's test for post hoc comparisons.

total sample was male. In 1997 (baseline), before the introduction of USI, there was no measurable iodine in salt. The UI and GR were 28 μg/L and 45%, respectively, indicating moderate-to-severe IDD (1). Significantly more young children (aged 5–9 y) than older children (aged 10–14 y) were goitrous ($P < 0.0001$; **Table 2**). In early 1998, the USI program was introduced. By November 1998, the mean (± SD) iodine concentration in household salt had increased to 11 ± 9 μg/g, and the UI had increased to 86 μg/L ($P < 0.0001$). There was a small, nonsignificant reduction in thyroid size compared with baseline, and the GR remained high, with 84% of children affected (Table 2). Although either palpation or ultrasonography was used to measure the GR in 1997, only ultrasonography was used in 1998. The increase in the GR between 1997 and 1998 was probably an artifact reflecting the increased sensitivity of ultrasonography to detect mildly enlarged thyroids (4, 9). In 1999, the mean iodine concentration in household salt was 25 μg/g, and the UI was 161 μg/L, indicating adequate iodine intake (Table 1). This was associated with a significant 35% reduction in mean thyroid size compared with baseline ($P < 0.0001$) but only an 8% reduction in the GR (Table 2). In 2000, the GR had decreased significantly to 42%, one-half the prevalence in 1998 ($P < 0.0001$). In 2001, 4 y after USI, although mean thyroid size had decreased 56% from baseline ($P < 0.0001$), 29% of children remained goitrous.

Over the course of the study, there was an age shift in the distribution of goiter (Table 2). Before iodization, the GR was significantly higher in younger (5–9 y of age) than in older (10–14 y of age) children ($P < 0.0001$). At 2, 3, and 4 y after USI, although the GR had decreased significantly from baseline in both younger and older children, the decrease was greater in the younger children ($P < 0.0001$). As modeled by logistic regression, at 2, 3 and 4 y after iodization, the GR was significantly greater in the older than in the younger children ($P < 0.0001$), and the group difference increased with time ($P < 0.0001$ comparing time and group model relative to the

TABLE 2
Thyroid volume and prevalence of goiter in 5–14-y-old children in Côte d'Ivoire before and after introduction of iodized salt[1]

	Before iodization	After iodization			
	1997 (n = 419)	1998 (n = 204)	1999 (n = 641)	2000 (n = 507)	2001 (n = 526)
Thyroid volume (mL)[2]	8.3 (3.1–20.1)[a]	7.1 (2.1–21.4)[a]	5.4 (1.4–39.7)[b]	3.9 (1.2–14.5)[c]	3.4 (1.1–22.5)[d]
5–9-y-olds	7.2 (4.9–17.9)[a]	6.7 (2.1–19.3)[a]	4.7 (1.4–16.0)[b]	3.1 (1.2–10.9)[c]	2.7 (1.1–10.4)[d]
10–14-y-olds	9.3 (7.0–20.1)[a]	8.3 (3.5–21.4)[a]	7.1 (1.9–39.7)[b]	5.6 (1.7–14.5)[c]	5.4 (1.7–22.5)[c]
No. of subjects with goiter[3]	188 [45][a]	172 [84][b]	486 [76][b]	207 [42][a]	152 [29][c]
Females	72 [40][a]	67 [76][b]	132 [65][b]	57 [34][a]	46 [24][c]
Males	116 [49][a]	105 [91][b]	354 [80][b]	150 [46][a]	106 [31][c]
5–9-y-olds	112 [52][a]	119 [84][b]	295 [71][c]	120 [37][d]	71 [19][e]
10–14-y-olds	76 [38][a]	53 [84][b]	291 [83][b]	87 [54][c]	81 [52][c]

[1] Values in the same row with different superscript letters are significantly different, $P < 0.05$. Significance of post hoc comparisons is given in the text.
[2] Median; range in parentheses. Compared by using ANOVA on logarithmically transformed data: time × treatment, $P < 0.0001$; time × age, $P < 0.0001$. Tukey's test for post hoc comparisons.
[3] Percentage in brackets. Compared by using chi-square test: time × treatment, $P < 0.0001$; time × age, $P < 0.0001$; time × sex, $P < 0.0001$.

time-only model). After 4 y, the GR in the younger children had fallen to 19%, compared with 52% in the older children ($P < 0.0001$). The percentage decrease in mean thyroid size after 4 y was significantly greater in the younger (63%) than in the older (41%) children ($P < 0.0001$), and the group difference increased with time ($P < 0.0001$ comparing time and group model relative to the time-only model).

Mean serum thyroxine and median serum thyrotropin were within the normal reference ranges both before and after USI, and there was no significant change in mean serum thyroxine over the course of the study (Table 1). However, in response to salt iodization, there was a significant decrease in median serum thyrotropin and in the number of children with elevated thyrotropin concentrations ($P < 0.0001$). The prevalence of potential goitrogenic factors was measured in 1997 and again in 1999. The prevalence of iron-deficiency anemia in 1997 and 1999 was 27% and 19%, respectively. In 1997, mean (±SD) serum selenium was only 15.4 ± 8.4 μg/L, and 92% of children had low serum selenium concentrations. Deficiencies of vitamin A were common, with 64% and 45% of children having low concentrations of serum retinol in 1997 and 1999, respectively. In 1997, because of high levels of cassava consumption, the median urinary iodine-urinary thiocyanate (UI-thiocyanate) ratio was only 1.8 μg/mg, indicating a risk of exacerbation of goiter (24).

DISCUSSION

In this study, USI rapidly normalized the UI, decreased the mean thyrotropin concentration, and reduced the proportion of children with an elevated thyrotropin concentration. These effect indicators are highly sensitive to recent changes in iodine intake (1). In contrast, 4 y after USI, the GR was 29%, indicating moderate-severe IDD by WHO/ICCIDD/UNICEF criteria (1). Cross-sectional studies also found a discrepancy between a normal UI and an elevated GR in the immediate post-USI period (3, 4). There are several potential reasons for the long delay in the GR response. Endemic goiter is caused by increased stimulation of the thyroid by thyrotropin in an effort to maximize the utilization of available iodine. In the present study, the mean thyrotropin concentration decreased significantly in the first year and remained in the low-normal range thereafter. Only 2–3% of children exhibited elevated thyrotropin concentrations after the first year. Thus, persisting thyrotropin overstimulation does not appear to explain the high GR. Although it has been suggested that long-standing goiters may become autoimmune (25), we have measured thyroid antibodies in these children and found no evidence of increased thyroid autoimmunity (MB Zimmermann, unpublished data, 2002). Compared with the 2 previous years, in 2001 salt iodine concentrations and the UI had fallen significantly and were only marginally sufficient. This may have contributed to the delay in the GR response. Also, multiple goitrogens present in the children may have blunted the effect of USI. Deficiencies of selenium, iron, and vitamin A were common and may have impaired the thyroid response to iodine repletion (12, 26). Cassava is one of the staple foods of this region, and median UI-thiocyanate ratios were low (< 3 μg/mg), indicating an increased risk of exacerbation of goiter by thiocyanate (24).

A potential limitation of the GR in children as a USI effect indicator is the possibility that enlarged thyroids in children who were iodine deficient during the first years of life may not regress completely after the introduction of iodized salt (27). If true, achieving a GR < 5% in children aged 6–12 y may require that the children grow up under conditions of iodine sufficiency. This implies that the lag time to normalization of thyroid size and GR in children aged 10–12 y could be a decade or more. In support of the premise that enlarged thyroids in children growing up in IDD-affected areas may not regress completely, our data indicate a clear age shift in the GR in the present study (Table 2). Before iodization, significantly more younger children than older children were goitrous. In response to 4 y of adequate iodine supply, the mean percentage decrease in thyroid size from baseline was significantly greater in the younger than in the older children. This was reflected in a significantly higher GR in the older children at 2, 3, and 4 y after the introduction of USI. After 4 y, the GR in the younger children was nearly one-third that of the older children (19% compared with 52%).

Several authors reported trials of iodized oil in children and used ultrasonography to measure thyroid response. In Algerian schoolchildren, iodized oil providing iodine doses of 960 mg (orally) or 480 mg (intramuscularly) decreased mean thyroid volume 23–29% after 1 y (28). In Côte d'Ivoire, 200 mg I as oral iodized oil given to school-aged children was associated with a 41% reduction in mean thyroid volume after 1 y (29). Other studies evaluated the effect on the GR of smaller doses of oral iodine given as a potassium iodide solution or iodized salt. Oral administration of potassium iodide solution providing 30 mg I monthly or 8 mg biweekly to school-aged children in Zimbabwe significantly reduced thyroid size, as measured by ultrasonography over 13 mo (30). In South African children, after 1 y of mandatory USI, the UI was normalized but the GR by palpation was unchanged (3). In a small study in Chinese schoolchildren comparing iodized oil to iodized salt, provision of iodized salt normalized the GR after 18 mo (11). However, the children were only mildly iodine deficient at baseline and the UI throughout the intervention was maintained > 200 μg/L. In contrast, our subjects were severely iodine deficient at baseline and USI maintained the UI at a lower concentration of 86–161 μg/L.

The strengths of the present study were its prospective design and long follow-up, as well as the use of ultrasonography to measure thyroid size and updated WHO/ICCIDD references to classify goiter. Our data emphasize that the GR may be a poor IDD indicator up to 4 y after the introduction of USI because it reflects chronic, rather than immediate, iodine deficiency. Additional studies on changes in the GR after the introduction of iodized salt in other countries with varying conditions would be valuable. Compared with the rapid reduction in thyroid size from large doses of iodized oil, shrinkage and remodeling of the goitrous thyroid in response to lower iodine doses associated with USI appear to be much more gradual. Despite this, the GR is a sensitive long-term indicator of the success of an iodine program, and normalization of the GR in children previously affected by IDD have been reported by sustained USI programs (2, 31). Encouraged by rapid improvements in salt iodine concentrations and the UI, governments and program managers monitoring USI effect may expect a parallel improvement in the GR. It is important to recognize the limitation of the GR in judging the short-term efficacy of salt iodization programs.

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