Thyroid size and goiter prevalence after introduction of iodized salt: a 5-y prospective study in schoolchildren in Côte d’Ivoire

Michael B Zimmermann, Sonja Y Hess, Pierre Adou, Toni Toresanni, Rita Wegmüller, and Richard F Hurrell

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.

KEYWORDS 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.

1 From the Human Nutrition Laboratory, Swiss Federal Institute of Technology, Zürich, Switzerland (MBZ, SYH, RW, and RFH); the Ministry of Health, Abidjan, Côte d’Ivoire (PA); and the Department of Endocrinology, University of Zürich Children’s Hospital, Zürich, Switzerland (TT).
2 Supported by the Thrasher Research Fund (Salt Lake City) and the Swiss Federal Institute of Technology (Zürich, Switzerland).
3 No reprints available. Address correspondence to MB Zimmermann, Human Nutrition Laboratory, Institute of Food Science and Nutrition, Swiss Federal Institute of Technology Zürich, Seestrasse 72/Postfach 474, CH-8803 Rüschlikon, Switzerland. E-mail: michael.zimmermann@ilw.agrl.ethz.ch.
Received March 12, 2002.
Accepted for publication June 12, 2002.
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 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, Germany). SYH 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 μmol/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.

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 householders 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 (ZnP), 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 μUI thyrotropin/L and 65–165 nmol thyroxine/L. Hemoglobin was measured with an AcT8 Counter (Beckman Coulter, Krefeld, Germany). ZnP 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 ZnP/mol heme.

Iron deficiency was defined by multiple criteria: SF < 15 μg/L or TfR > 8.5 mg/L + ZnP > 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.

Normal reference values are > 3 μg UI/mg thiocyanate (23), > 0.70 μmol serum retinol/L, and 65–105 μg serum Se/L.
household salt was 25 ± 126 g/g, and the UI was 161 ± 7.4 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 1**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Before iodization</th>
<th>After iodization</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–9</td>
<td>8.8 ± 2.7</td>
<td>8.5 ± 2.5</td>
</tr>
<tr>
<td>10–14</td>
<td>8.9 ± 2.3</td>
<td>8.8 ± 2.3</td>
</tr>
</tbody>
</table>

---

**TABLE 2**

| 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before iodization</th>
<th>After iodization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>8.8 ± 2.7</td>
<td>8.5 ± 2.5</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>231:188</td>
<td>215:204</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.27 ± 0.17</td>
<td>1.24 ± 0.19</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.9 ± 7.1</td>
<td>25.1 ± 6.7</td>
</tr>
<tr>
<td>Serum thyrotropin (mU/L)</td>
<td>2.2 (0.4–76.4)</td>
<td>1.2 (0.6–24.6)</td>
</tr>
<tr>
<td>Thyroid volume (mL)</td>
<td>137 ± 36</td>
<td>122 ± 26</td>
</tr>
<tr>
<td>Urinary iodine (μg/L)</td>
<td>28 (5–176)</td>
<td>86 (12–541)</td>
</tr>
<tr>
<td>Salt iodine (g/g)</td>
<td>&lt;2 [52]</td>
<td>7.5 ± 1.2 [94]</td>
</tr>
</tbody>
</table>

---

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. Mean ± 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 one-way ANOVA on logarithmically transformed data across years (NS).
7. Compared by using chi-square test.
8. 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.
9. 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.
10. 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 thyrotrpin 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 thyrotrpin and in the number of children with elevated thyrotrpin 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 thioctanate (UI-thioctanate) 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 thyrotrpin concentration, and reduced the proportion of children with an elevated thyrotrpin 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 thyrotrpin in an effort to maximize the utilization of available iodine. In the present study, the mean thyrotrpin concentration decreased significantly in the first year and remained in the low-normal range thereafter. Only 2–3% of children exhibited elevated thyrotrpin concentrations after the first year. Thus, persisting thyrotrpin 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. Only 2–3% of children exhibited elevated thyrotrpin concentrations after the first year. Thus, persisting thyrotrpin overstimulation does not appear to explain the high GR. It is important to recognize the limitation of the GR in judging the short-term efficacy of salt iodization programs.

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 long-term efficacy of salt iodization programs.

We thank the participating children and teachers, IB Ghato (Public Health, Côte d’Ivoire), C Zeder (Swiss Federal Institute of Technology Zürich), and C Flowers (University of Kansas Medical Center, Kansas City). Each of the authors contributed to the study design. The fieldwork and data collection were done by MBZ, SYH, PA, and RW. The statistical analysis was done by MBZ and SYH. MBZ, SYH, TT, and RFH completed the final data analysis. The manuscript was written by MBZ and SYH and edited by PA, TT, RW, and RFH. None of the authors has a financial or personal conflict of interest in regard to this study.
REFERENCES


