Serum Thyroglobulin and Urinary Iodine Concentration Are the Most Appropriate Indicators of Iodine Status and Thyroid Function under Conditions of Increasing Iodine Supply in Schoolchildren in Benin

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ABSTRACT Iodine deficiency control programs have greatly reduced iodine deficiency disorders worldwide. For monitoring changes in iodine status, different indicators may be used. The aim of this study was to evaluate the suitability of indicators of iodine status and thyroid function, thyroglobulin (Tg), thyroid-stimulating hormone (TSH) and free thyroxine (FT4) in serum, thyroid volume and urinary iodine concentration, in iodine-deficient schoolchildren under conditions of increasing iodine supply. The study was established as a double-blind, placebo-controlled oral administration of a single dose of iodized oil to schoolchildren (7–10 y old), living in an iodine-deficient area of Benin, with an observation period of 10 mo. However, 3–4 mo after supplementation, iodized salt became available in the area. The study population therefore comprised an iodized oil–supplemented group and a nonsupplemented group, both of which had variable, uncontrolled intakes of iodized salt during the last 6 mo of the study. Initial mean serum concentrations of TSH and FT4 were within the normal range, whereas serum Tg concentration, urinary iodine concentration and thyroid volume were indicative of moderate-to-severe iodine deficiency. At the end of the study, all indicators had improved significantly, except thyroid volume, which had decreased only in the supplemented group. The supplemented group also still had significantly lower serum Tg and higher urinary iodine concentrations than the nonsupplemented group. Serum Tg and urinary iodine concentrations are the indicators most influenced by a changing iodine supply. Current normal reference ranges of serum concentrations of TSH and FT4 are too wide for detecting iodine deficiency in this age group. J. Nutr. 131: 2701–2706, 2001.

KEY WORDS: • iodine deficiency • indicators • schoolchildren • Benin

In the context of initiatives to achieve universal salt iodization, a number of population-based studies have addressed the question of which indicators best reflect improvement in iodine status and thyroid function (1–4). Although thyroid-stimulating hormone (TSH)3 is widely used to screen neonates for congenital hypothyroidism, there have been doubts about its specificity in older children and adults when assessing hypothyroidism induced by iodine deficiency (5). Several studies have shown that although urinary iodine concentrations and thyroid volumes were indicative of iodine deficiency in the populations studied, both serum TSH and free thyroxine (FT4) concentrations were within normal ranges (2,3). Thyroid volume, serum thyroglobulin (Tg) concentration and urinary iodine concentration have all been suggested as useful indicators for measuring improvement in iodine status after iodine prophylaxis. However, all three have their own characteristics and limitations. Normal ranges for thyroid volume have been established (6,7), but this indicator reflects long-standing hypothyroidism and does not respond rapidly to changes in iodine status. Serum Tg concentration is thought to respond quickly to stimulation of the thyroid, increasing when iodine supply to the thyroid is depleted and returning to normal levels when the supply is sufficient. However, Tg immunoassays show large interlaboratory and interassay variability, which makes it difficult to establish a universal normal range and cut-off points for distinguishing between different degrees of iodine deficiency (8,9). Urinary iodine concentration is not a direct measure of thyroid function, but reflects recent iodine intake and thyroid hormone catabolism. Thus, population groups, even if currently found to be in the mildly deficient to normal range of urinary iodine concentration, may still experience serious functional consequences of iodine deficiency in the preceding period.

As part of a study on iodine status and mental performance...
in schoolchildren aged 7–10 y in an iodine-deficient area of Benin, West Africa, the five indicators mentioned above were used to measure the effects of changing iodine supply on iodine status and thyroid function, both at the beginning of the study in 1995 and 1 y later, when iodized salt had become available to the population. The aim of this study was to evaluate the suitability of these indicators under conditions of increasing iodine supply by comparing their responses and examining their interrelationships.

SUBJECTS AND METHODS

Study area and subjects. The study was carried out in four villages in the district of Basila, province of Atacora, in northern Benin, where prevalence rates of goiter in schoolchildren aged 6–12 y varied from 20 to 60% (Doh, A. and Ategbo, E. A. Préalèvement de la carence en iode dans l’Atakora; unpublished report, 1994). The villages had neither electricity nor clean drinking water. The population was engaged mainly in subsistence farming. Polygamy was common and levels of parental education were low (Table 1). Children from standards 2 and 3 in the four primary schools in the study area were considered for enrollment. In two of the four schools, girls were not selected because they had received an oral dose of iodized oil in the previous year. A total of 211 children were selected. Because 13 children had left school or moved out of the area by the end of the intervention period, data from 198 children are presented. The study was approved by the health and education authorities of the province of Atacora, Benin and by the Medical Ethics Committee of the Division of Human Nutrition and Epidemiology of Wageningen University. The aim of the study was explained to local administrative and traditional authorities, parents and teachers. Having obtained verbal approval from local authorities, the parents and the parents-teachers association, all children selected were examined by a physician. Several children with skin or respiratory infections, and malaria were treated. No children were excluded on health grounds.

Study design. The study was set up as a randomized, double-blind, placebo-controlled intervention. After baseline measurements, children were stratified by school, school class and sex and subsequently matched on the basis of similar age and height-for-age. From each pair of children, one child was randomly allocated to one of two groups. The groups were then randomly allocated to receive either a dose of iodized oil (Lipiodul UF 7; 540 g/L) or a placebo (propyosed oil), both provided by Guerbet Laboratories (Aulnay-sous-Bois, France) and administered as a single oral dose (1.0 mL) with a Swift 7 dispenser (English Glass Company, Leicester, UK) in January 1996. The codes were broken after the completion of the final test.

In this paper we describe the performance of different indicators in a group that had received an iodized oil supplement ("supplemented group") and in a group that had received a placebo ("nonsupplemented group"). In addition, both groups had access to iodized salt for the last 6 mo of the 10-mo observation period because iodized salt (containing ~50 mg KIO₃/kg salt) began to appear in the markets in the study area alongside noniodized salt ~3–4 mo after supplementation.

Somatom and biochemical indicators. Blood, urine and anthropometric variables as well as thyroid volume were measured at baseline in October-November 1995. All measurements were repeated in October-November 1996. Additional urine samples were collected 1 wk and 5 mo after supplementation, i.e., in January and May 1996.

Venous blood was drawn from the antecubital vein, immediately followed by the application of one drop of whole blood onto a filter paper card (Schleicher & Schuell, grade 903; Keene, NH). These cards were air-dried for 1–2 h and packed in polyethylene bags before being frozen. Hemoglobin was assessed using a portable hemoglobinometer (HemoCue, Helsingborg, Sweden). Serum samples were prepared and frozen before transport. Casual samples of urine (~25 mL) were collected early in the morning and some crystals of thymol were added. Blood spot cards and frozen samples of urine and serum were transported to the Micronutrient Research Laboratory, University of Ghana at Legon, Accra, Ghana for analysis of urinary iodine [chloric acid digestion followed by Sandell-Kolhoff reaction (10)], TSH in blood spots [Spectra Screen Dried Blood TSH Enzyme Immunoassay Kit; IMM Diagnostica, Berlin, Germany] and TSH (immunoluminometric assay; Brahms Diagnostica, Berlin, Germany). The intra- and inter-assay CV were 3.6 and 6.4% for FT4, 2.4 and 4.5% for TSH and depending on the concentration, 6–7 and 7–10%, respectively, for Tg.

A subsample of the sera (n = 23) was analyzed for selenium concentration at Rowett Research Institute, Aberdeen, UK using a fluorimetric assay method with dianmonophosphate complexing and an International Atomic Energy Agency blood standard (IAEA Vienna, Austria).

Anthropometric measurements were made in duplicate. Height was measured to the nearest 1 mm, using a microtome (Stanley Tool, Besançon, France). Weight was measured to the nearest 0.25 kg using a spring scale. Thyroid volume was measured by one investigator only (T.vdB.) with a portable ultrasound scanner (Aloka SSD 500; Aloka Japan) with a 5-MHz transducer.

Data analysis. Prints of the ultrasound images of the thyroid glands were examined by a pediatric thyroidologist (T.V.) and either accepted or rejected for inclusion in the data set on the basis of criteria pertaining to clarity of the surface outlines and proper positioning of the gland. Thyroid volumes were calculated using the following formula: volume of one lobe (mL) = 0.479 × maximum thickness × maximum width × length (cm) (6). Body surface area was calculated using the following formula: body surface area (m²) = W°.₄₂₅ × H°.₇₅₅ × 71.84 × 10⁻⁴, where W is the weight in kg and H the height in cm (11). Anthropometric indices were calculated using Epi-Info (version 6.02; CDC, Atlanta, GA).

The Kolmogorov-Smirnov test was used to determine whether variables were normally distributed. Variables were log-transformed if not normally distributed. Student’s t test was used to assess changes between groups. The paired t test was used to assess changes in the variables over time. Correlation and multiple regression analyses were carried out to determine the interdependence of the indicators used. Factor analysis (12) was applied to examine underlying structures in the data set and determine whether the variables used could be combined into a single or a reduced number of composite measures representing “iodine status,” as has also been done for iron status (13).

All data were processed and analyzed using SPSS/PC software (SPSS-Windows 8.0; SPSS, Chicago, IL).

RESULTS

Anthropometric characteristics. Of the children, 33% had Z-scores for height-for-age < –2 SD of National Center for Health Statistics (NCHS) reference (14), indicating stunted growth in this population, whereas 17% had low weight-for-

TABLE 1

<table>
<thead>
<tr>
<th>Characteristics of subjects</th>
<th>n (boys/girls)</th>
<th>Age, yr</th>
<th>Weight-for-age Z-score</th>
<th>Education, yr</th>
<th>Characteristics of family</th>
<th>Family size, n</th>
<th>Education of parents, yr</th>
<th>Size of landholding, m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (boys/girls)</td>
<td>198 (168/30)</td>
<td>8.9 ± 1.2</td>
<td>-1.64 ± 0.96</td>
<td>-1.34 ± 0.72</td>
<td>2.8 ± 0.8</td>
<td>14.4 ± 7.6</td>
<td>1.4 ± 0.8</td>
<td>1.2 ± 0.6</td>
</tr>
</tbody>
</table>

1 Results are expressed as means ± SD or n.
Thyroid volume, TSH concentration
Serum thyrotropin, Serum free thyroxine, pmol/L

The children had both a low serum concentration of FT4 ( ). Mean serum TSH and FT4 concentrations

Table 2

Whole could be considered moderately to severely iodine de-

surface, thyroid volume measurements showed that 52% of the

other indicators except thyroid volume. When related to body

Serum TSH concentration was significantly correlated with all

measured, serum Tg concentration was significantly correlated

CIDD (5), the baseline urinary iodine concentration of 0.16

On the basis of criteria established by WHO/UNICEF/IC-

shown). 

Mean serum TSH and FT4 concentrations

Correlations between indicators of iodine status before or 10 mo after iodine supplementation

Biochemical and ultrasound characteristics at baseline.

On the basis of criteria established by WHO/UNICEF/IC- CIDD (5), the baseline urinary iodine concentration of 0.16 

μmol/L (20.3 μg/L) indicated that the study population as a

whole could be considered moderately to severely iodine de-

fficiency (Table 2). Mean serum TSH and FT4 concentrations

were within the normal reference range (15–17), but 5% of the

children had both a low serum concentration of FT4 (<10

pmol/L) and a high serum concentration of TSH (>). Approximately 15% of the children had a serum FT4 concentra-

<10 pmol/L, and 11% of the children had a serum TSH concentra-

>4.4 μU/mL. Of the different indicators measured, serum Tg concentration was significantly correlated with all other indicators, except TSH in blood spots (Table 3). Serum TSH concentration was significantly correlated with all other indicators except thyroid volume. When related to body surface, thyroid volume measurements showed that 52% of the

children had goiter, i.e., a thyroid volume above the upper

limit of normal. Thyroid volume was significantly correlated

with body surface ( = 0.271; P = 0.002), but not with age. The various indicators measured showed a somewhat poorer iodine status and thyroid function in older children than in younger children, but differences were significant (P < 0.05) only for urinary iodine concentration (data not shown). The mean serum selenium concentration in a subsample of 23 children was 28 ± 12 μg/L.

Regression analysis with thyroid volume as the dependent variable and the other iodine indicators as the independent variables did not result in a meaningful regression variate. When Tg was taken as the dependent variable, all other indicators except thyroid volume were significant predictor variables (P < 0.05). This regression variate may be presented as follows: Y = 2.825 + 0.237 X1 − 0.025 X2 − 0.210 X3; where Y = log (Tg); X1 = log (TSH); X2 = FT4; X3 = log (urinary iodine concentration). Model R2 = 0.323; adjusted R2 = 0.308. F(5,143) = 22.24, P < 0.0001 (for the units used, see Table 2).

Biochemical characteristics at end of the study. 

By the end of the study period, all indicators showed significant improvement in the study population as a whole (Table 2). The proportion of children with a low serum concentration of FT4 or a high serum concentration of TSH had decreased to 2% and 1%, respectively. The proportion of children with goiter had decreased to 27%. Correlations between the different variables were no longer significant, except for the negative correlations between serum Tg and urinary iodine concen-

tration and between thyroid volume and serum TSH concen-

tration (Table 3).

Factor analysis was carried out to determine whether one or more underlying latent variables could be identified and whether the variables used in the study could be combined into a single or reduced number of composite measures (“fac-

tors”). Through this procedure, factors that represent the original variable as much as possible, i.e., that carry high loadings of these variables may be formed. If the factors are expected to be independent of one another, orthogonal rotation is applied to maximize the loadings of the variables. If they are not expected to be independent of one another, as is the case in this study, oblique rotation is applied. Two factors remain:

with serum Tg and urinary iodine concentration loading 0.56

and 0.49 on these factors, respectively. Correlations between these factors were high (r = 0.65; P < 0.001). These factors were considered to represent the different aspects of iodine deficiency in children: Factor 1 is related to thyroid function and thyroid volume measurements, whereas Factor 2 is related to the urinary iodine concentration. The two factors explained 59% of the variance in the original variables.

TABLE 3

Correlations between indicators of iodine status before or 10 mo after iodine supplementation

Pearson correlation coefficients

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
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<th>After</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
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<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tg (serum)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2 TSH (serum)</td>
<td>0.43***</td>
<td>0.12</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 TSH (whole blood spots)</td>
<td>0.07</td>
<td>NA</td>
<td>0.33***</td>
<td>NA</td>
<td>1.00</td>
<td>NA</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>4 Free T4 (serum)</td>
<td>-0.34***</td>
<td>-0.02</td>
<td>-0.34***</td>
<td>-0.02</td>
<td>-0.20**</td>
<td>NA</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Thyroid volume</td>
<td>0.27**</td>
<td>0.07</td>
<td>0.16</td>
<td>-0.17*</td>
<td>0.07</td>
<td>NA</td>
<td>-0.06</td>
<td>-0.03</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Urinary iodine</td>
<td>-0.50***</td>
<td>-0.26***</td>
<td>-0.37***</td>
<td>-0.08</td>
<td>-0.09</td>
<td>NA</td>
<td>0.21</td>
<td>0.03</td>
<td>-0.14</td>
<td>-0.06</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Nonnormally distributed variables were log-transformed.
2 Significance of correlation coefficients: * P < 0.05; ** P < 0.01; *** P < 0.001.
3 Horizontal numbers 1−6 refer to the numbered indicators in the left column.
4 TSH in whole blood spots was assessed only at baseline.

Abbreviations: Tg, thyroglobulin; TSH, thyroid-stimulating hormone; NA, not available; T4, thyroxine.
the first factor and serum FT4 concentration loading on the second factor. Serum TSH concentration loaded initially on both factors, but at the end of the study it loaded primarily on the second factor (Table 4). Similar results were found when younger and older children (above and below the median age) were compared. From the communalities and the percentage of trace, it may be concluded that the factors formed on the basis of the scores on the four variables at the beginning of the study show a better "fit" than those at the end of the observation period. This corresponds with the disappearance of significant correlations between most variables at the end of the study as shown in Table 3.

**Supplemented vs. nonsupplemented groups.** Initially, the supplemented and nonsupplemented groups were fully comparable. After the oral administration of the iodized oil, the mean urinary iodine concentration in the supplemented group improved (Fig. 1A). The difference between the two groups became smaller when 3–4 mo later the whole population began to have access to iodized salt alongside noniodized salt, and the mean urinary iodine concentration improved in the nonsupplemented group. No quantitative data on the use of the iodized salt were obtained, but at the end of the observation period the proportion of nonsupplemented children with urinary iodine concentrations <0.16 μmol/L had decreased from one half to about one fifth. At the end of the study (12 mo after the baseline survey; 10 mo after supplementation) the supplemented and the nonsupplemented groups did not differ in serum TSH and FT4 concentrations or thyroid volume, but supplemented and nonsupplemented groups did not differ after the baseline survey; 10 mo after supplementation) the mean urinary iodine concentration improved in the supplemented group (300 and 56%, respectively) and to a lesser extent in the serum concentrations of TSH and FT4 (33 and 18%, respectively). Serum Tg concentration and urinary iodine concentration were closely associated not only when iodine deficiency was moderate to severe, but also when it was mild. Moreover, under conditions of moderate-to-severe iodine deficiency, serum Tg concentration was correlated with all other indicators of thyroid function except TSH in blood spots. As shown by others (18), serum Tg concentrations are raised as a consequence of elevated serum TSH concentrations; unlike TSH, and FT4, however, Tg is not involved in any feedback regulatory mechanisms. Thus both urinary iodine concentration and Tg are independent measures of iodine supply to the body. Unfortunately, there is great interlaboratory variation in the measurement of serum Tg concentration. At the present time, cut-off values are based on values obtained in individual laboratories. Therefore, it will be necessary for methods for estimating serum Tg concentration to be standardized before they can be applied widely in monitoring iodine status in programs to control iodine deficiency.

**TABLE 4**

Oblique-rotated factor matrix of indicators of iodine status before or 10 mo after iodine supplementation

<table>
<thead>
<tr>
<th>Oblique-rotated loadings</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Communality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Serum thyroglobulin concentration</td>
<td>0.82</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Serum thyrotropin concentration</td>
<td>0.66</td>
<td>0.06</td>
<td>0.68</td>
</tr>
<tr>
<td>Serum free thyroxine concentration</td>
<td></td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Urinary iodine concentration</td>
<td>−0.86</td>
<td>−0.78</td>
<td>0.78</td>
</tr>
<tr>
<td>Sum of squares (Eigenvalue)</td>
<td>2.11</td>
<td>1.28</td>
<td>0.82</td>
</tr>
<tr>
<td>Percentage of trace</td>
<td>52.8</td>
<td>32.0</td>
<td>20.5</td>
</tr>
</tbody>
</table>

1 Nonnormally distributed variables were log-transformed.
2 The loading refers to the correlation of the variable and the factor; only loadings ≥ 0.50 are included.
3 Communality refers to the amount of variance in a variable that is accounted for by the two factors together.
4 Proportion of the total variance to be explained.

**DISCUSSION**

Serum Tg and urinary iodine concentration were the most appropriate indicators for measuring change in iodine status in this population. The change in iodine supply to this population through iodized oil supplementation and consumption of iodized salt was reflected in considerable changes in the concentration of iodine in urine and of Tg in serum (300 and 56%, respectively) and to a lesser extent in the serum concentrations of TSH and FT4 (33 and 18%, respectively). Serum Tg concentration and urinary iodine concentration were closely associated not only when iodine deficiency was moderate to severe, but also when it was mild. Moreover, under conditions of moderate-to-severe iodine deficiency, serum Tg concentration was correlated with all other indicators of thyroid function except TSH in blood spots. As shown by others (18), serum Tg concentrations are raised as a consequence of elevated serum TSH concentrations; unlike TSH, and FT4, however, Tg is not involved in any feedback regulatory mechanisms. Thus both urinary iodine concentration and Tg are independent measures of iodine supply to the body. Unfortunately, there is great interlaboratory variation in the measurement of serum Tg concentration. At the present time, cut-off values are based on values obtained in individual laboratories. Therefore, it will be necessary for methods for estimating serum Tg concentration to be standardized before they can be applied widely in monitoring iodine status in programs to control iodine deficiency.

Serum concentrations of TSH, the recommended indicator for use in screening newborn infants, and of FT4 cannot be regarded as appropriate indicators for detecting moderate-to-severe iodine deficiency in children of this age. On the basis of these concentrations, the iodine status of the study population would have been classified as within the normal reference range (3.15–17), both at the beginning and at the end of the study period. Under the conditions of low iodine intake as found in our study area, it is plausible to assume that thyroid hormone production has been affected negatively, causing a temporary increase in serum TSH concentration. This could induce initially increased bloodflow through the thyroid and subsequently hypertrophy and hyperplasia. These mechanisms would result in increased production of thyroxine (T4). Once T4 production has increased to satisfactory levels, serum TSH concentrations would fall. This may explain why mean serum concentrations of FT4 and TSH were found to be within the normal range. However, changes in serum FT4 and TSH concentrations after increased iodine intake were still significant. Moreover, the proportions of children whose serum
concentrations of FT4 were too low or whose serum concentrations of TSH were too high were significantly diminished. This suggests that the normal reference range of these indicators may be too wide to detect mild-to-moderate degrees of iodine deficiency, or alternatively, that conclusions with respect to thyroid function under such conditions may not be drawn on the basis of results of these two indicators alone.

As suggested by several authors (19–22), the “normal” concentration of FT4 may also have been the result of a lower deiodination of T4 because of a concurrent severe selenium deficiency. In a subsample \((n = 23)\) of our study population, the mean serum selenium concentration was only \(28 \pm 12\) \(\mu\)g/L, whereas in studies in healthy child populations in Europe, values were found to range from 60 to \(>100\) \(\mu\)g/L (22). A normal serum concentration of FT4 in turn could account for the normal serum concentration of TSH.

Although mean serum TSH concentration at baseline was within the normal range, TSH measurements in whole-blood spots showed that 42% of the children had concentrations \(>5\) mU/L whole blood. Although there are doubts about the applicability of the latter cut-off point in age groups other than neonates (5), this rate may still be considered high and concurs with our data on goiter rates and urinary iodine concentration, which indicated a moderate-to-severe public health problem. However, the correlation between the concentrations of TSH in serum and whole blood, although significant, was not very high \((r = 0.33)\). Furthermore, although initial serum TSH concentration was correlated with all other indicators except thyroid volume, the TSH concentration in blood spots was correlated only with FT4. Therefore, the validity of the filter paper method for whole-blood TSH may be questioned.

Comparison of the performance of the various indicators in the supplemented and nonsupplemented groups 10 mo after supplementation shows that thyroid volume and serum concentrations of TSH and FT4 were not significantly different between these two groups. Because the whole population began to have access to iodized salt \(\sim3–4\) mo after supplementation, children in the supplemented group did not maintain their better iodine status, except with respect to the concentration of Tg in serum and iodine in urine. It would only be a matter of time for the nonsupplemented children to catch up fully with the supplemented children. It is noteworthy, however, that even after both groups had access to iodized salt for \(\sim6\) mo, serum Tg concentration and urinary iodine concentration were still significantly better in the supplemented group. This further supports our proposition that Tg and urinary iodine concentration are more sensitive indicators than TSH or FT4.

Correlations between all indicators of iodine status decreased considerably when iodine status improved. At the end of the follow-up period they were still stronger in the nonsupplemented group than in the supplemented group. When serum indicators of iodine status reach normal values and show less variation, correlations between indicators are likely to disappear.

Over the study period, all indicators except thyroid volume changed significantly in the study population as a whole. Thyroid volumes were significantly reduced only in the sup-

![FIGURE 1](image)

**FIGURE 1** Indicators of iodine status and thyroid function in children who received a placebo (open bars) or a single oral dose of iodized oil (closed bars) in January 1996. Values are means ± sd. Both groups had access to iodized salt during the last 6 mo of the follow-up period of 10 mo. **Panel A**: urinary iodine concentration \((n = 198\) in 1995 and in 1996). **Panel B**: serum free thyroxine (FT4) concentration \((1995: n = 193, 1996: n = 198)\). **Panel C**: serum thyroglobulin (Tg) concentration \((1995: n = 194, 1996: n = 198)\). **Panel D**: serum thyroid-stimulating hormone (TSH) concentration \((1995: n = 154; 1996: n = 198)\). **Panel E**: thyroid volume \((1995: n = 131; 1996: n = 146)\). Statistical significance of difference with placebo group at same time point using Student’s t test is indicated as follows: a, \(P < 0.05\); b, \(P < 0.01\); c, \(P < 0.001\). Statistical significance of difference with values in 1995 of same group using paired t test is indicated as follows: d, \(P < 0.05\); e, \(P < 0.01\); f, \(P < 0.001\).
plemented group. Earlier studies showed different rates of reduction of thyroid volume after iodized oil administration, some showing a rapid response (23,24) and others a more modest or gradual response (2,25,26). Reduction in goiter sizes and goiter rates after the introduction of iodized salt have generally been modest. In a study in Italy (27), iodized salt prophylaxis prevented the development of goiter in children born after the introduction of the salt, but was less effective in reducing goiter size in children born earlier. In a recent study carried out in South Africa (28), the prevalence of goiter was not reduced 1 y after the introduction of mandatory salt iodization, whereas urinary iodine concentration was indicative of an improved iodine supply. Similar results were also reported from Indonesia (29). Therefore, thyroid volume is not appropriate as an indicator for measuring change in iodine status in the short term.

Current recommendations suggest that thyroid volumes be related to body surface rather than to age in populations with a high prevalence of malnutrition because of its effect on growth and development of the thyroid gland (7). This was confirmed in our study, in which the older tertile was significantly more undernourished (lower weight-for-age) and stunted (lower height-for-age) than was the younger tertile, thus providing an explanation why thyroid volume was not related to age but was related to body surface. The age differences in degree of malnutrition probably may be ascribed to a period of severe drought and hunger in the study area in 1987.

The results of this study show that "iodine status," like iron status, is a concept not easily captured in one indicator. It may well be that concomitant selenium deficiency would explain the relatively high serum concentration of FT4 and the relatively low serum concentration of TSH in this iodine-deficient population. In population-based studies, depending on the age of the target group, different combinations of indicators should be used. Under the conditions found in Benin, serum Tg concentration together with urinary iodine concentration are in our opinion the best combination of indicators for school-aged children aged 7–10 y.

ACKNOWLEDGMENTS

We are grateful to D. Alnwick (then at UNICEF, New York) for providing us with the portable ultrasound scanner used in this study. We also thank J. R. Arthur, Rowett Research Institute, Aberdeen, UK for carrying out selenium analyses in a subsample of serum from our study population.

LITERATURE CITED


