Assessing Iodine Status and Monitoring Progress of Iodized Salt Programs[1]

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ABSTRACT Despite remarkable progress in the control of the iodine deficiency disorders (IDD), they remain a significant global public health problem. Assessing the severity of IDD and monitoring the progress of salt iodization programs are cornerstones of a control strategy. Because thyroid size decreases only gradually in response to iodized salt, the goiter rate in children may be a poor IDD monitoring indicator for several years after the introduction of salt iodization. During this period, the goiter rate reflects chronic iodine deficiency, and will be inconsistent with measurements of urinary iodine. Thyroglobulin is a promising new biochemical indicator for monitoring thyroid function after the introduction of iodized salt. Recent development of a dried blood spot thyroglobulin assay makes sample collection practical even in remote areas. Interpretation of thyroid volume data from ultrasound surveys requires valid references from iodine-sufficient populations, but defining normal values for thyroid size in children has been difficult. New international reference criteria for thyroid volume were published recently and can be used for goiter screening in the context of IDD monitoring. Ensuring sustainability is one of the great remaining challenges in the global fight to eliminate IDD. A recent cohort study demonstrated the vulnerability of children in IDD-affected areas to even short-term lapses in iodized salt programs. J. Nutr. 134: 1673–1677, 2004.

KEY WORDS: • iodine • monitoring • goiter • thyroglobulin • thyroid

Current Global Prevalence of Iodine Deficiency. The WHO has developed a new global database on the prevalence of iodine deficiency disorders (IDD)[3] (1). Using urinary iodine (UI) data from 1993 to 2003, the WHO estimated the current national and worldwide prevalence of iodine deficiency. Goiter rates were used to compare the 2003 results with those of the previous decade, for which figures for UI were not available. For each country, the estimate of iodine deficiency was derived using 2 criteria, i.e., the representative level of the sample (e.g., national, regional, or local) and the population groups surveyed (e.g., school-aged children, pregnant women, adults).

UI data were collected for 92% of the world's population. Defined as a UI < 100 μg/L, nearly 2 billion individuals have inadequate iodine nutrition; of these, 285 million are school-aged children (**Table 1**). The prevalence of iodine deficiency in school-aged children is 36.4%. Universal salt iodization (USI) is the recommended strategy for IDD control, and the lowest prevalence of iodine deficiency is found in the Americas (10.1%), where the proportion of households consuming iodized salt is the highest in the world (90%). Surprisingly, the highest prevalence of iodine deficiency is in Europe (59.9%), where the proportion of households consuming iodized salt is the lowest (27%), and most countries have weak or nonexistent national programs (2).

The WHO used a new approach to derive these estimates. They extrapolated from a population indicator (median UI) to individual status, to define the number of individuals affected. This means that in a country such as Switzerland designated "iodine sufficient" on the basis of a median UI in children of $\sim$110 μg/L (2), nearly 50% of children are "iodine deficient" according to the WHO estimate. This inconsistency may lead to confusion when assessing IDD control programs. Nevertheless, the overall findings clearly indicate that IDD remains an important public health problem in many areas of the world. This comprehensive database will help track progress toward the goal of global IDD elimination adopted by the 1990 World Health Assembly (3).

The Discrepancy between Goiter Rate and Urinary Iodine Concentration during the Early Phase of a Salt Iodization Program. After implementation of USI, careful monitoring of progress towards elimination of IDD is essential. The principal indicator of effect in a population is the median UI, because it is highly sensitive to recent changes in iodine intake (4). A second indicator is thyroid volume (Tvol) as reflected by the goiter rate (GR). In endemic areas, although thyroid size decreases in response to increases in iodine intake, Tvol and GR may not return to normal for months or years after correction of iodine deficiency (5). During this period, GR is a poor indicator because it reflects a population's history of iodine nutrition but not its present iodine status.

Several countries have reported a discrepancy between UI and GR after introduction of USI (6,7). For example, in South African children, after 1 y of mandatory USI, UI normalized but GR was unchanged (6). Despite this, the GR is an important long-term indicator of the success of USI. The ultimate goal of USI is to not simply to increase UI, but to eliminate thyroid dysfunction caused by iodine deficiency. The reduction of GR to $<5\%$ in school-aged children indicates the disappearance of IDD as a significant public health problem (4). Normalization of the GR in children was reported by sustained USI programs (5,8). In a small study in Chinese

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[3] Abbreviations used: BSA, body surface area; DBS, dried whole blood spots; ICCIDD, International Council for the Control of the Iodine Deficiency Disorders; IDD, iodine deficiency disorders; GR, goiter rate; T4, thyroxine; Tg, thyroglobulin; TSH, thyrotropin; Tvol, thyroid volume; UI, urinary iodine; USI, universal salt iodization.

TABLE 1

Global and regional prevalence of iodine deficiency (UI < 100 μg/L) in all age groups and in school-aged children (6–12 y) in 2003[1]

WHO region	Individuals with UI < 100 μg/L	
	All	School-aged children
	$n \times 10^{-3}$ (%)	
Africa	260,325 (42.6)	49,465 (42.3)
Americas	75,081 (9.8)	9955 (10.1)
Eastern Mediterranean	228,451 (54.1)	40,224 (55.4)
Europe	435,452 (56.9)	42,215 (59.9)
Southeast Asia	624,013 (39.8)	95,628 (39.9)
Western Pacific	365,332 (24.0)	47,056 (25.7)
Total	1,988,654 (35.2)	284,543 (36.4)

[1] Adapted from (3).

schoolchildren affected by mild IDD, GR was reduced from 18 to 5–9% after 18 mo of salt iodization (9).

A recent 5-year prospective study in West Africa documented the time course and pattern of changes in GR and UI after introduction of USI in an area of long-standing, severe endemic goiter (10). In western Côte d'Ivoire, Tvol by ultrasound, UI, thyrotropin (TSH), and thyroxine (T4) were measured in school-aged children 6 mo before the introduction of iodized salt and annually for 4 y thereafter. UI increased within 1–2 y from 28 to 161 μg/L, indicating adequate iodine intake. Mean serum TSH concentration and the number of children with an elevated TSH decreased rapidly. Four years after the introduction of USI, mean thyroid size had decreased –56%. The percentage decrease in mean thyroid size was significantly greater in the younger (−63%) than the older children (−41%). There was a significant age shift in the distribution of goiter in the sample. At baseline, GR was significantly higher in younger (5- to 9-y-olds) than in older children (10- to 14-y-olds). At 2, 3, and 4 y after salt iodization, GR was significantly higher in the older compared with the younger children (at 4 y: 52 vs. 19%), and the difference increased with time. Four years after normalization of UI, 29% of children remained goitrous.

There are several potential reasons for the long delay in GR response after USI. Endemic goiter results from increased thyroid stimulation by TSH to maximize the utilization of available iodine. In the Ivorian study (10), mean TSH concentration decreased rapidly and only 2–3% of children exhibited elevated TSH levels after y 1. Thus, persisting TSH hyperstimulation did not explain the high GR. Although long-standing goiters may become autoimmune (11), thyroid autoimmunity is rare in school-aged children after the introduction of USI (12). Aghini-Lombardi et al. (13) suggested that enlarged thyroids in children who were iodine deficient during the first years of life may not regress completely after introduction of USI. If true, this suggests that to achieve a GR < 5% in children may require that they grow up under conditions of iodine sufficiency. This implies that the lag time to complete normalization of GR in children aged 10–12 y could be a decade or more.

The data emphasize that GR may be a poor IDD indicator for several years after introduction of USI, primarily due to persisting goiter in older children. During this period GR reflects chronic, rather than immediate, iodine deficiency. Governments and program managers monitoring the effect of USI, encouraged by rapid improvements in salt iodine levels and UI, may expect a parallel improvement in GR. It is important to recognize the limitation of GR in judging the short-term efficacy of salt iodization programs.

Dried Blood Spot Thyroglobulin as a Promising New IDD Indicator. The major biological indicators of response to USI are UI, GR, and TSH (4). However, all have limitations. UI is a sensitive indicator of recent iodine intake, but not thyroid function. Because thyroid size decreases only slowly after iodine repletion, GR in children is a poor IDD indicator for several years after beginning USI (10). TSH is a sensitive IDD indicator only in the newborn period (4). An additional indicator of thyroid status, sensitive to recent changes in iodine nutrition and applicable in children, would be valuable.

Thyroglobulin (Tg), the most abundant thyroid protein, is a key precursor in the production of thyroid hormone and is thyroid specific (14). In areas of endemic goiter, the major determinants of serum Tg are thyroid cell mass and TSH stimulation (15). Intervention studies examining the potential of Tg as an indicator of the effect of IDD in response to iodized oil and potassium iodide showed that Tg falls rapidly with iodine repletion, and that Tg is a more sensitive indicator of iodine repletion than TSH or T4 (16–19). However, commercially available assays measure serum Tg, which requires venipuncture, centrifugation, and frozen sample transport, which may be difficult in remote, IDD-affected areas.

A recent study described the development and testing of a Tg assay on dried whole blood spots (DBS) (20). A sandwich fluoroimmunometric serum Tg assay was adapted for DBS use and validated in school-aged children. The correlation between serum and DBS Tg assays was excellent ($r = 0.98$). Intra-assay imprecision (CV) was 6.3%, and the day-to-day CV was <20% over the range of the calibration curve. However, the SD of difference comparing DBS and serum Tg was 3.8 μg/L, and the limits of agreement at the 95% significance level were −8 and 11 μg/L. Because Tg concentrations in iodine-sufficient and mild-to-moderately iodine-deficient children are distributed mainly between 5 and 40 μg/L, the inherent measurement error was high for Tg concentrations at the lower end of the usual range. Also, there was higher variability in sample duplicates than in control duplicates, indicating that sampling of whole blood spots can be a source of measurement bias.

In a 1-y prospective study in goitrous 6- to 15-y-old Moroccan children, the DBS assay was used to measure Tg before and after USI introduction (20). UI, Tvol, TSH, and T4 were measured and regression was done on Tg. The children were severely iodine deficient before USI; the median UI was 17 μg/L and GR was 72% (15). The median Tg (range) fell rapidly from a baseline of 24.5 (0–328.8) to 6.2 (0–83.1) and 4.4 (0–47.1) μg/L at 5 and 12 mo, respectively. According to WHO/ICCIDD recommended cutoff values for serum Tg, a median < 10 μg/L at 5 and 12 mo indicates normalization of iodine status (21). Regression of Tg on UI, TSH, T4, and Tvol was done at each time point. Tg was significantly correlated with TSH and T4 only at baseline. The regression of UI and Tvol on Tg was significant at baseline and at 5 mo ($P < 0.01$).

These findings suggest that Tg is a promising biochemical indicator of thyroid function in children after USI introduction (20). It could complement use of UI (recent iodine intake) and Tvol (long-term anatomic response). Use of a DBS assay makes acquisition and transport of samples practical even in remote areas. However, several questions must be resolved before Tg can be widely adopted as an IDD indicator.

Major limitations include large interassay variability and poor reproducibility, even with the use of Community Bureau of Reference standardization (15). This has made it difficult to establish normal ranges and/or cutoff values to distinguish severity of iodine deficiency. Another question is the need for concurrent measurement of anti-Tg antibodies to avoid potential underestimation of Tg. Although a common source of Tg assay error in thyroid cancer (15), it is unclear how prevalent anti-Tg antibodies are in iodine-deficient children, or whether they are precipitated by iodine prophylaxis (12,22,23).

New WHO Reference Criteria for Thyroid Volume by Ultrasound. The GR in school-age children is an indicator of the severity of the IDD in a population. A GR $\geq$ 5% in this age group indicates a public health problem (4). Inspection and palpation have traditionally been used to classify goiter. However, in areas of mild-to-moderate IDD, the sensitivity and specificity of palpation are poor (24), and measurement of Tvol using ultrasound is preferable (21). Thyroid ultrasound is noninvasive, quickly performed (2–3 min per subject), and feasible even in remote areas using portable equipment.

Interpretation of Tvol data requires valid references from iodine-sufficient children. In 1997, the WHO and the International Council for the Control of the Iodine Deficiency Disorders (ICCIDD) proposed references for Tvol (25) based on data from European children (26). However, subsequent reports suggested that these references were too high. Tvol reported from iodine-sufficient children in the United States, Switzerland, and Malaysia (27–29) were distinctly smaller than those of the European children from whom the 1997 reference data were derived (26). The larger Tvols in the 1997 reference data may have been partially a residual effect of iodine deficiency that existed in many European countries up to the early 1990s (30). However, in 2000, a WHO/ICCIDD workshop on thyroid ultrasound uncovered a large systematic measurement bias in the 1997 references (+30% volume at all ages and all body surface areas) (31). Updated references were then published, derived from the 1997 references corrected for the systematic difference found during the workshop, but these were considered provisional (32).

In a recent large, multicenter study, Tvol was measured in 6- to 12-y-old children living in areas of long-term iodine sufficiency in North and South America, Central Europe, the Eastern Mediterranean, Africa, and the Western Pacific (33). Sites were selected on 5 continents and included children from most of the major ethnic groups around the world. The sample of 3529 children was evenly divided between boys and girls at each age. The range of median UI was 118–288 μg/L among the 6 study sites. Measurements of Tvol were done by 2 experienced examiners using validated technique. Data were log transformed, used to calculate percentiles based on the Gaussian distribution, and then transformed back to the linear scale. Age- and body surface area (BSA)-specific 97th percentiles for Tvol were calculated for boys and girls. There were significant differences in age- and BSA-adjusted mean Tvol between sites, suggesting that population-specific references in countries with long-standing iodine sufficiency may be more accurate than a single international reference. However, overall differences in age- and BSA-adjusted Tvol between sites were modest relative to the population and measurement variability, supporting the use of a single, site-independent set of references.

These new international reference values for Tvol by ultrasound are recommended for goiter screening during IDD monitoring. However, users should be mindful of 2 important issues. First, compared with previous references for Tvol (25,32,34), the new references are more conservative. For example, for boys, both the age- and BSA-specific P97 Tvol in the new references (33) are ~20% smaller than the corrected 1997 references (32). The new references will therefore produce higher estimates of GR when used to interpret Tvol measurements from IDD monitoring programs. Second, the references are applicable for goiter screening if Tvol is determined by a standard method (35). Thyroid ultrasound is subjective in that finding and measuring the maximum diameters requires judgment and experience. Differences in technique (e.g., the pressure applied with the transducer) and estimation of thyroid anatomy (e.g., inclusion of the thyroid isthmus and/or capsule thickness) can produce interobserver errors in Tvol as high as 26% (31). To improve the reliability and comparability of Tvol data used in IDD monitoring, it is important that a standardized approach be adopted worldwide.

The Critical Issue of Sustainability: Thyroid Dysfunction Returns Rapidly if a USI Program Falters. Of the 130 countries affected by IDD, 84% have national legislation on salt iodization in place or in draft form (4). Worldwide, sustainability of IDD control programs has become a major focus. In several countries in which IDD had been eliminated by USI, control programs faltered, and IDD recurred (8,36,37). In Guatemala, a previously effective iodized salt program deteriorated; currently, only 46% of households are receiving iodized salt, the median UI is 72 μg/L, and new cases of cretinism have appeared (8). In regions of the former USSR, successful, long-term iodized salt programs have lapsed, and IDD has returned. In Azerbaijan, the current GR is 86% and the median UI is 54 μg/L, indicating moderate-to-severe IDD (36). A similar pattern of IDD recurrence was also demonstrated in Kazakhstan, Kyrgyzstan, and neighboring countries (8). In addition, IDD may be reemerging in industrialized countries previously thought to be iodine sufficient, such as Australia and New Zealand (38,39). If an iodized salt program lapses, children may be particularly vulnerable.

A recent cohort study described the changes in thyroid function after sudden interruption of USI in school-aged children in an area of endemic goiter (40). Moroccan children (6–16 y old) with severe IDD received iodized salt for 1 y. Because of practical and financial constraints, salt iodization was discontinued. The children were followed for 14 more mo, with measurements of UI, TSH, T4, Tg, and Tvol. One year after introduction of iodized salt, median UI and Tg had normalized, mean Tvol had decreased by 34%, and median TSH and mean T4 had increased. The improvements in thyroid function reversed rapidly when salt iodization was discontinued; 5 mo after USI lapsed, the median UI had declined to 19 μg/L, indicating the return of severe iodine deficiency. The marked reduction in thyroid volume (−34%) during USI was entirely reversed 14 mo post-USI, and the prevalence of hypothyroidism was higher than before USI. Median TSH and Tg rebounded to levels twice that before salt iodization. Overall, these data suggest that IDD recurrence was characterized by a marked increase in TSH stimulation in an effort to maintain normal levels of circulating thyroid hormone. Although in most children this adaptive response was able to maintain normal T4 levels, 10% of children in this study were hypothyroid 14 mo after salt iodization ceased (**Fig. 1**).

The findings of this study should be interpreted carefully. First, the rapid return of thyroid dysfunction after discontinuation of USI occurred after only 1 y of iodized salt distribution. In populations provided iodized salt for longer periods, it

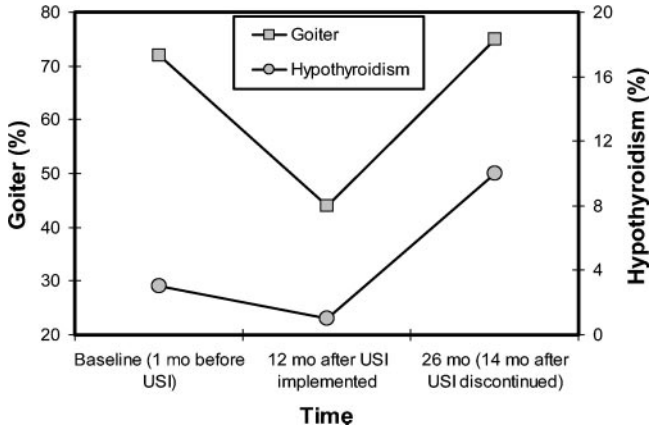

FIGURE 1 The prevalence of goiter and hypothyroidism in a cohort of 6- to 16-y-old school children (n = 159) at baseline before introduction of iodized salt, at 12 mo after introduction of iodized salt, and at 14 mo after discontinuation of iodized salt (26 mo from baseline). Data are from (40).

is possible that thyroid function would be better preserved if iodine intake were to fall. However, the children in this study had average daily intakes of ~150–300 μg iodine for 1 y; thus, they should have received adequate iodine to completely replenish intrathyroidal stores (10–20 mg) (41). These findings may not apply to adults. Children may be more sensitive to fluctuations in iodine nutrition because they have lower thyroid stores of iodine and higher rates of iodine turnover (41).

These data demonstrate the vulnerability of children in IDD-affected areas to even short-term lapses in iodized salt programs (40). In many countries with newly established IDD control programs, great progress has been made through USI introduction. Yet these programs are fragile and depend on a strong, long-term commitment from national governments, donors, consumers, and the salt industry (4). Governments that enthusiastically set up IDD control programs may afterward shift attention and funding to other health problems without providing for program sustainability. Ensuring sustainability is one of the great remaining challenges in the global fight to eliminate IDD.

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