

Rapid relapse of thyroid dysfunction and goiter in school-age children after discontinuation of salt iodization¹⁻³

Michael B Zimmermann, Rita Wegmüller, Christophe Zeder, Toni Torresani, and Noureddine Chaouki

ABSTRACT

Background: In programs to control iodine deficiency disorders (IDD), sustainability is a major concern. IDD has recently recurred in countries where salt iodization programs have lapsed.

Objective: The objective of the study was to describe the evolution of thyroid dysfunction after the discontinuation of salt iodization in a cohort of children in an area of severe endemic goiter.

Design: Moroccan children (aged 6–16 y, $n = 159$) with severe IDD received iodized salt (IS) for 1 y. Because of practical and financial constraints, including a lack of infrastructure and electricity at the production site, salt iodization abruptly ceased. The children were followed for another 14 mo, and concentrations of urinary iodine, thyrotropin, total thyroxine, and thyroglobulin and thyroid volume were measured.

Results: Before iodization, median urinary iodine was 18 $\mu\text{g/L}$, 88% of children had elevated serum thyroglobulin concentrations, and 72% were goitrous. One year after the introduction of IS, median urinary iodine and thyroglobulin concentrations had normalized, mean thyroid volume had decreased by 34%, and median thyrotropin and mean total thyroxine concentrations were improved. Five months after the discontinuation of salt iodization, median urinary iodine had fallen to 20 $\mu\text{g/L}$. Fourteen months after the discontinuation of salt iodization, the rate of goiter was again similar to the rate before salt iodization; median thyrotropin and thyroglobulin concentrations were sharply higher than before the introduction of IS ($P < 0.001$); and the prevalence of hypothyroidism was 10%, compared with 3% before the introduction of IS ($P < 0.001$).

Conclusions: In IDD-affected areas, cessation of salt iodization is associated with a rapid deterioration of thyroid function in school-age children. These findings underline the importance of sustainability in IDD control and the vulnerability of children to even short-term lapses in IS programs. *Am J Clin Nutr* 2004;79:642–5.

KEY WORDS Iodine, deficiency, fortification, salt, goiter, thyroid, children

INTRODUCTION

There has been remarkable global progress in the control of iodine deficiency disorders (IDD) through the iodization of salt. In 84% of the 130 countries affected by IDD, national legislation setting up salt iodization programs is in place or in draft form (1). It is estimated that 68% of households worldwide now have

access to iodized salt (IS; 1). For many countries with IDD control programs, sustainability has become a major focus (2). In several countries where IDD had been eliminated by IS programs—including Colombia, Guatemala, Azerbaijan, and other countries of the former Soviet Union—control programs faltered, and IDD recurred (3–5). In addition, IDD may be reemerging in industrialized countries, such as Australia and New Zealand, that were previously thought to be iodine sufficient (6, 7).

Chronic iodine deficiency markedly alters thyroid metabolism (8). Low circulating thyroxine concentrations increase thyrotropin secretion by the pituitary. Thyrotropin stimulation of the thyroid increases that gland's ability to trap iodine and preferentially secrete triiodothyronine (8). Thyrotropin stimulation also alters the morphology of the thyroid and produces hyperplasia and goiter. In children affected by IDD, the provision of IS reverses most of these changes, although increased thyroid volume may persist even after correction of iodine deficiency (9). If an IS program then lapses and IDD recurs, children may be particularly vulnerable because they have lower stores of iodine in the thyroid and higher rates of iodine turnover than do adults (8). Cross-sectional studies from regions where IS programs were discontinued found a return of goiter and low median urinary iodine (UI) excretion (3, 4) and new cases of cretinism (4).

The populations of the mountains of northern Morocco are affected by severe IDD, and the rate of goiter among schoolchildren is 50–72% (10, 11). In a recent intervention trial in this region, an IS program was introduced and carefully monitored for 1 y (12). Unfortunately, because of financial and practical barriers, salt iodization was abruptly discontinued. In this study, we describe longitudinal changes in iodine nutrition and thyroid metabolism associated with sudden cessation of iodine prophylaxis in a cohort of school-age children in an area of severe endemic goiter.

¹ From the Human Nutrition Laboratory, Swiss Federal Institute of Technology (MBZ, RW, and CZ), and the Department of Endocrinology, University Children's Hospital (TT), Zürich, Switzerland, and the Ministry of Health, Rabat, Morocco (NC).

² Supported by the Nestlé Foundation (Lausanne, Switzerland), the Thrasher Research Fund (Salt Lake City), and the Swiss Federal Institute of Technology (Zürich, Switzerland).

³ Reprints not available. Address correspondence to M Zimmermann, Laboratory for Human Nutrition, Swiss Federal Institute of Technology, Seestrasse 72, PO Box 474, CH-8803 Rüschlikon, Switzerland. E-mail: michael.zimmermann@ilw.agrl.ethz.ch.

Received August 25, 2003.

Accepted for publication October 28, 2003.

SUBJECTS AND METHODS

The study was conducted in villages of the Brikcha Rural Commune, an area of endemic goiter in the Rif Mountains of northern Morocco. Although Morocco has national legislation setting up salt iodization programs and the Health Ministry actively promotes the use of IS, only 42% of the population has access to IS (13). There are a plethora of small salt producers, many working in remote areas, for whom iodization is technically or practically difficult. Salt for the villages in this study is produced in drying ponds by a small local cooperative, and it has a native iodine content < 2 ppm (12). Mean daily salt intake among school-age children in this region is 7.3–11.6 g (12). The subjects in this study were children aged 6–16 y ($n = 159$) from 2 primary schools. Informed oral consent was obtained from the school directors, the teachers, and the parents of the children. The Swiss Federal Institute of Technology Zürich and the Ministry of Health of Morocco gave ethical approval for the IS intervention study (0–12 mo). After the IS program lapsed, the same institutions gave approval for the follow-up measurements. The study took place between January 2001 and April 2003.

At baseline, before the introduction of IS, the children's weight and height were measured, and a casual spot urine sample was collected for measurement of UI. The thyroid volume was measured by using a portable Aloka SSD-500 Echocamera (Aloka, Mure, Japan) with a high-resolution 7.5-MHz linear transducer. Whole blood obtained by venipuncture was spotted onto filter paper for measurement of thyrotropin, total thyroxine (TT4), and thyroglobulin concentrations. For 1 y, each household with children enrolled in the study received a monthly 2-kg portion of IS (12). The iodine was added to the local salt as potassium iodide (Sigma & Aldrich, Buchs, Switzerland) in a proportion of 25 μg iodine/g salt, and it was dry-mixed into the salt with the use of a rotating-drum electric mixer (ELTE 650; Engelsmann, Ludwigshafen, Germany). For monitoring, 50-g aliquots ($n = 8$) of the salt were taken at both 5 and 12 mo, and iodine content was measured. At 5 and 12 mo, all baseline measurements in the children were repeated.

The IS study was paid for by a limited grant that could afford to support iodization and distribution of the local salt for only 1 y. At the end of the 1-y study, a local committee working with the salt producer had planned to install the permanent infrastructure to continue the IS program. However, because of financial and practical constraints (primarily, a lack of electricity at the production site), this was not done. Five months after the discontinuation of the IS program, we returned to the schools and collected spot urine samples ($n = 71$ out of the total cohort of 159) and household salt samples ($n = 12$). Fourteen months after the discontinuation of the IS program, household salt samples ($n = 12$) were collected, and the baseline measurements were repeated in all children.

Laboratory analyses

Urine and blood samples were transported on ice to the provincial hospital laboratory. Urine samples were aliquoted and frozen at -20°C until they were analyzed. UI was measured by using a modification of the Sandell-Kolthoff reaction (14). At UI concentrations of 47 and 79 $\mu\text{g}/\text{L}$, the CV of this assay in our laboratory is 10.3% and 12.7%, respectively. Salt iodine content was measured in 10-g salt aliquots dissolved in distilled water by using a modification of the Sandell-Kolthoff reaction (14). The

limit of detection is 2 μg I/L; samples with a lower concentration were assigned a value of 0. We analyzed dried blood spots on filter paper for whole-blood thyrotropin, serum TT4, and thyroglobulin content with the use of immunoassays (15, 16). Normal reference values are < 3.7 mU thyrotropin/L, 65–165 nmol TT4/L, and < 10 μg thyroglobulin/L. Hypothyroidism was defined as ≥ 3.7 mU thyrotropin/L and < 65 nmol TT4/L. Thyroid volume was calculated by using the method of Brunn et al (17). The same investigator (MZ) performed all ultrasound measurements during the study. To estimate intraobserver variability, duplicate thyroid volume measurements were done in 25 children; the mean (\pm SD) variability was $3.7 \pm 2.0\%$. New reference values from the World Health Organization for thyroid volume in school-age children according to sex and body surface area (BSA) were used to define goiter (18).

Statistical analyses

Data processing and statistics were done by using PRISM3 software (version 3.0; GraphPad, San Diego) and EXCEL 97 software (version XP 2002; Microsoft, Redmond, WA). Repeated-measures analysis of variance was done to compare changes in UI, thyrotropin, TT4, and thyroglobulin concentrations and thyroid volume; Tukey's test was used for post hoc comparisons. Variables not normally distributed (ie, UI, thyrotropin, and thyroglobulin concentrations) were logarithmically transformed before analysis. Proportions were compared by using McNemar's test. To reduce the influence of age and sex on the variable of thyroid volume, the volumes were standardized by using current reference values (18) according to the equation

Standardized thyroid volume

$$(\text{Tvol}_s) = \log(\text{Tvol}) - \log(\text{P50Tvol}_s)/\text{SD} \quad (1)$$

where P50Tvol_s is the mean reference volume for a certain BSA. To reduce the effects of variability among persons, the percentage change in thyroid volume from baseline ($\% \Delta \text{Tvol}_s$) was calculated for each child before means were derived. Significance was set at $P < 0.05$.

RESULTS

The sample included 75 girls and 84 boys with a mean (\pm SD) age at baseline of 10.1 ± 1.9 y. The UI, thyrotropin, TT4, and thyroglobulin concentrations; the thyroid volume; and the rates of goiter and hypothyroidism before the introduction of IS, during the IS program, and after the discontinuation of the IS program are shown in **Table 1**. Before the IS program, the children were severely iodine deficient: the median UI concentration was 18 $\mu\text{g}/\text{L}$, serum thyroglobulin was elevated in 88% of the children, and 72% were goitrous (1). The native salt iodine content was below the detection limit of our assay. After 5 mo of the IS program, median UI and thyroglobulin concentrations had normalized. After 1 y of the IS program, mean thyroid volume had decreased by 34%, and median thyrotropin and mean TT4 concentrations had improved significantly from their pre-IS program values ($P < 0.01$).

The improvements in thyroid function reversed rapidly when the IS program was discontinued (Table 1). Five months after discontinuation of the IS program, the median UI concentration had fallen to 19 $\mu\text{g}/\text{L}$, which indicated a return of severe iodine deficiency. Fourteen months after the discontinuation of the IS

TABLE 1

Changes in concentrations of urinary iodine, salt iodine, thyrotropin, total thyroxine, and thyroglobulin; thyroid volume (by ultrasound); and goiter rate in 6–16-y-old Moroccan school children ($n = 159$) during provision of iodized salt for 12 mo and at 5 and 14 mo after discontinuation of salt iodization¹

	Baseline (before iodization)	5 mo after introduction of iodization	12 mo after introduction of iodization	17 mo (5 mo after discontinuation of iodization)	26 mo (14 mo after discontinuation of iodization)
Urinary iodine ($\mu\text{g/L}$) ²	18 (0–124) ^{3a}	180 (22–432) ^b	181 (14–451) ^b	19 (0–133) ^a	20 (0–178) ^a
Urinary iodine (%)					
< 20 $\mu\text{g/L}$	57	2	4	53	51
< 50 $\mu\text{g/L}$	88	15	13	84	86
< 100 $\mu\text{g/L}$	95	29	22	97	95
Salt iodine ($\mu\text{g/g}$)	< 2	24.1 \pm 3.9 ^d	23.4 \pm 4.2	< 2	< 2
Whole-blood thyrotropin (mU/L) ⁵	0.8 (0.5–6.2) ^a	1.2 (0.4–14.9) ^a	0.6 (0.4–1.8) ^b	NA	1.9 (0.3–13.4) ^c
Serum total thyroxine (nmol/L) ⁶	82.4 \pm 17.4 ^a	90.1 \pm 19.8 ^b	92.3 \pm 12.6 ^b	NA	85.4 \pm 19.0 ^a
Hypothyroidism [n (%)] ⁷	5 (3) ^a	2 (1) ^b	1 (1) ^b	—	16 (10) ^c
Serum thyroglobulin ($\mu\text{g/L}$) ²	24.2 (0–321.6) ^a	6.3 (0–83.1) ^b	4.5 (0–47.0) ^b	NA	49.1 (1–862.5) ^c
> 10 $\mu\text{g/L}$ [n (%)] ⁷	140 (88) ^a	37 (23) ^b	19 (12) ^c	—	142 (89) ^a
Thyroid volume (mL) ⁶	8.9 \pm 3.3 ^a	8.3 \pm 2.6 ^a	5.9 \pm 2.3 ^b	NA	9.3 \pm 1.9 ^a
Change from baseline (%)	—	–6.3 \pm 11.5	–34.0 \pm 9.5	—	0.6 \pm 8.2
Goiter [n (%)] ⁷	114 (72) ^a	97 (61) ^b	70 (44) ^c	NA	119 (75) ^a

¹ NA, not available. 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.

^{2,5} Compared by repeated-measures ANOVA on log-transformed data (Tukey's test for post hoc comparisons): ² $P < 0.0001$, ⁵ $P < 0.001$.

³ Median; range in parentheses (all such values).

⁴ $\bar{x} \pm \text{SD}$ (all such values).

⁶ Compared by repeated-measures ANOVA, $P < 0.0001$ (Tukey's test for post hoc comparisons).

⁷ Compared by using McNemar's test.

program, the median thyrotropin concentration and the prevalence of hypothyroidism were significantly higher than they were before the IS program ($P < 0.001$). Mean thyroid volume and the prevalence of goiter did not differ significantly from those before the IS program. Median thyroglobulin had rebounded strongly, to a concentration twice that before the IS program ($P < 0.001$).

DISCUSSION


Cross-sectional studies of lapsed IS programs have reported a recurrence of goiter and low UI concentrations. In Guatemala, a previously effective IS program deteriorated, and currently, only 46% of households have access to IS, the median UI concentration is 72 $\mu\text{g/L}$, and new cases of cretinism have appeared (3). In many countries of the former USSR, successful, long-term IS programs have lapsed, and IDD has recurred. For example, in Azerbaijan, the current prevalence of goiter in children is 86%, and the median UI concentration is 54 $\mu\text{g/L}$, which indicate moderate to severe IDD (4). A similar pattern of IDD recurrence has also appeared in Kazakhstan, Kyrgyzstan, and neighboring countries (3).

This longitudinal cohort study confirms the findings of previous cross-sectional studies (3, 4) on the adverse effects of a lapsed IS program in an area of severe IDD. Discontinuation of salt iodization was associated with a rapid return of thyroid dysfunction in school-age children. Fourteen months after the IS program was discontinued, the UI concentration, the thyroid volume, and the prevalence of goiter had relapsed to pre-IS program values. The rapid drop in median UI is not surprising, because UI is highly sensitive to recent changes in iodine intake (1). Although changes in thyroid volume lag behind changes in UI concentration (19), the marked reduction in thyroid volume (–34%) during the IS program was entirely reversed 14 mo after

discontinuation of the IS program. This finding emphasizes the sensitivity of thyroid volume during childhood to fluctuations in iodine intake. The main goitrogenic stimulus during iodine deficiency is thyrotropin. After the discontinuation of the IS program, median thyrotropin and thyroglobulin concentrations rebounded strongly, reaching concentrations twice those before salt iodization. In areas of endemic goiter, elevated serum thyroglobulin reflects thyrotropin hyperstimulation and thyroid hyperplasia (16, 20). Overall, these data suggest that IDD recurrence is characterized by a marked increase in thyrotropin stimulation in an effort to maintain normal concentrations of circulating thyroid hormone. Although in most children this adaptive response maintained normal TT4 concentrations, 10% of children in this study were hypothyroid 14 mo after salt iodization ceased.

The findings of this study are subject to several limitations. First, the rapid return of thyroid dysfunction after discontinuation of the IS program occurred after only 1 y of IS distribution. In populations provided IS for longer periods, it is possible that thyroid function would be better preserved if iodine intake decreased. However, the children in this study had average daily intakes of ≈ 150 – $300 \mu\text{g}$ iodine for 1 y, so they should have received adequate iodine to completely replenish intrathyroidal stores (ie, 10–20 mg) (8). Second, these findings may not apply to adults. Children may be more vulnerable to fluctuations in iodine nutrition because they have lower thyroid stores of iodine and higher rates of iodine turnover than do adults (8). Third, the children were ≈ 2 y older by the end of the study, and an age effect may have introduced bias into the serial measurements. However, an age effect is unlikely in serial comparisons of UI, TT4, thyrotropin, and thyroglobulin concentrations, and the thyroid volumes were age- and sex-standardized by using current reference values (18). Finally, the 5-mo post-IS median UI concen-

tration was measured in samples from 71 subjects and may not be representative of the entire cohort of 159 subjects.

These findings show the vulnerability of children in IDD-affected areas to even short-term lapses in IS programs. Iodine deficiency in young children is associated with poor cognition and impaired school performance (21). In many countries with newly established IDD control programs, great progress has been made through widespread introduction of IS. These programs are fragile, however, and they depend on a strong, long-term commitment from national governments, donors, consumers, and the salt industry (1). Governments that enthusiastically set up IDD control programs may afterward shift attention and funding to other health problems without providing for program sustainability. Ensuring the sustainability IS programs is one of the great remaining challenges in the global fight to eliminate IDD. 

We thank the participating children and their teachers and the staff at the Brikcha Health Center. Special thanks go to H Elfadel, R Rahmouni, M El-Yazami, and M Saïssi (Chefchaouen, Morocco) and to M-H Balsat and N Hurrell (Swiss Federal Institute of Technology, Zürich).

Each of the authors made substantial contributions to the study design, data collection, data analyses, and the writing or editing of the paper (or both). None of the authors had a personal or financial interest in the companies or organizations sponsoring this research, including advisory board affiliations.

REFERENCES

1. WHO/UNICEF/ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination. WHO/NHD/01.1. Geneva: World Health Organization, 2001.
2. Hetzel BS. Eliminating iodine deficiency disorders—the role of the International Council in the global partnership. *Bull World Health Organ* 2002;80:410–3.
3. Current IDD Status Database. International Council for the Control of Iodine Deficiency Disorders Website. Internet: <http://www.iccid.org> (accessed 12 August 2003).
4. Markou KB, Georgopoulos NA, Makri M, et al. Iodine deficiency in Azerbaijan after the discontinuation of an iodine prophylaxis program: reassessment of iodine intake and goiter prevalence in schoolchildren. *Thyroid* 2001;11:1141–6.
5. Dunn JT. Complacency: the most dangerous enemy in the war against iodine deficiency. *Thyroid* 2000;10:681–3.
6. Li M, Ma G, Boyages SC, Eastman CJ. Re-emergence of iodine deficiency in Australia. *Asia Pac J Clin Nutr* 2001;10:200–3.
7. Thomson CD, Woodruffe S, Colls AJ, Joseph J, Doyle TC. Urinary iodine and thyroid status of New Zealand residents. *Eur J Clin Nutr* 2001;55:387–92.
8. Delange F. Iodine deficiency. In: Braverman LE, Utiger RD, eds. *Werner & Ingbar's the thyroid: a fundamental and clinical text*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:295–316.
9. Aghini-Lombardi F, Antonangeli L, Pinchera A, et al. Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. *J Clin Endocrinol Metab* 1997;82:1136–9.
10. Zimmermann M, Saad A, Hess S, et al. Thyroid ultrasound compared with World Health Organization 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency. *Eur J Endocrinol* 2000;143:727–31.
11. Chaouki N, Ottmani S, Saad A, et al. Etude de prevalence des troubles dus à la carence iodée chez les enfants ages 6 à 12 ans au Maroc. [A prevalence study of iodine deficiency disorders in children aged 6–12 y in Morocco.] *Bull Epidemiol Morocco* 1996;1:2–23 (in French).
12. Zimmermann MB, Zeder C, Chaouki N, Saad A, Torresani T, Hurrell RF. Dual fortification of salt with iodine and microencapsulated iron: a randomized, double blind, controlled trial in Moroccan schoolchildren. *Am J Clin Nutr* 2003;77:425–32.
13. Ministry of Health of Morocco. Les carences en micronutriments: ampleur du problème et stratégies de lutte. [The micronutrient deficiencies: magnitude of the problem and strategies for control.] Rabat: Ministry of Health, 2001:25–9 (in French).
14. Pino S, Fang SL, Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. *Clin Chem* 1996;42:239–43.
15. Torresani T, Scherz R. Thyroid screening of neonates without use of radioactivity: evaluation of time-resolved fluoroimmunoassay of thyrotropin. *Clin Chem* 1986;2:1013–6.
16. Zimmermann MB, Moretti D, Chaouki N, Torresani T. Development of a dried whole blood spot thyroglobulin assay and its evaluation as an indicator of thyroid status in goitrous children receiving iodized salt. *Am J Clin Nutr* 2003;77:1453–8.
17. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. Volumetrie der Schilddrüsenlappen mittels Real-time-Sonographie. [Volumetric analysis of thyroid gland lobes by real-time ultrasound.] *Dtsch Med Wochenschrift* 1981;106:1338–40 (in German).
18. Zimmermann MB, Hess SY, Molinari L, et al. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. *Am J Clin Nutr* 2004;79:231–7.
19. Zimmermann MB, Hess SY, Adou P, Toresani T, Wegmüller R, Hurrell RF. Thyroid size and goiter prevalence after introduction of iodized salt: a 5-y prospective study in schoolchildren in Côte d'Ivoire. *Am J Clin Nutr* 2003;77:663–7.
20. Spencer CA. Thyroglobulin measurement: techniques, clinical benefits, and pitfalls. *Endocrinol Metab Clin North Am* 1995;24:841–63.
21. Tiwari BD, Godbole MM, Chattopadhyay N, Mandal A, Mithal A. Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. *Am J Clin Nutr* 1996;63:782–6.