

## COMMENT

# Effects of Chronic Iodine Excess in a Cohort of Long-Term American Workers in West Africa

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A cross-sectional survey of 102 Peace Corps volunteers in Niger, West Africa, in 1998 had previously demonstrated a high rate of thyroid dysfunction and goiter attributable to excess iodine from their water filters. The Peace Corps volunteers were followed-up a mean of 30 wk after they ceased using iodine-based water filtration systems. Goiter was present in 44% of subjects during excess iodine ingestion and in 30% after removal of excess iodine. Mean serum iodine decreased from 293  $\mu\text{g/liter}$  during excess iodine ingestion to 84  $\mu\text{g/liter}$  after cessation of excess iodine. Mean total serum  $T_4$  values increased from 100.4 to 113.3 nmol/liter (7.8 to 8.8  $\mu\text{g/dl}$ ). Mean

serum free  $T_4$  increased from 32.2 to 34.7 pmol/liter (2.5 to 2.7 ng/dl). Mean serum TSH decreased from 4.9 to 1.8 mU/liter. Mean serum thyroid peroxidase antibody levels decreased from 33,000 to 22,000 IU/liter (33 to 22 IU/ml).

We found that during prolonged excess iodine exposure there were marked increases in serum total iodine concentrations, and the prevalence of goiter, elevated serum TSH values, and elevated serum thyroid peroxidase antibody values increased. The prevalence of all abnormalities decreased after removal of excess iodine from the drinking water system. (*J Clin Endocrinol Metab* 87: 5499–5502, 2002)

PEACE CORPS VOLUNTEERS in Niger, West Africa, were noted to have a high prevalence of goiter from 1995–1998. Initial investigation revealed 39 suspected cases of thyroid abnormality. Peace Corps volunteers in many areas of Africa drink iodine-enriched water to avoid microbial contamination, and it was subsequently found that the two-stage iodine-resin ceramic filters in use in Niger delivered a mean concentration of 10 mg iodine/liter to the drinking water (1). There was no evidence of a high concentration of iodine in the diet, salt, medications, or nutritional supplements.

As the arid climate in Niger results in the daily consumption of 5–9 liters water, the volunteers consumed at least 50 mg iodine daily, which is approximately 300 times the daily U.S. Recommended Dietary Allowance (2). Urinary iodine excretion in this iodine-enriched population ranged from 392–153,780  $\mu\text{g/liter}$  (median, 5,048  $\mu\text{g/liter}$ ). Volunteers used the water purification devices described above for up to 32 months. After the discovery of this iodine overload, all iodine-based filters in Niger were discontinued, and other methods of purification were used (boiling the water or treating the water with micro-filtration and chlorine purification).

In May 1998, a cross-sectional survey of volunteers then in Niger was conducted just before removal of the excess iodine from the drinking water and, on the average, 30  $\pm$  11 wk later (range, 3–83 wk) in Niger or after return to the U.S. Goiter prevalence and levels of serum TSH and thyroid peroxidase (TPO) antibodies significantly decreased after removal of the

water filters and correction of the iodine excess, strongly suggesting that the iodine-induced abnormalities were not permanent.

## Subjects and Methods

### Study population

Of the 103 Peace Corps volunteers in Niger in May of 1998, 102 (99%) participated in the survey, and 1 declined. Data describing 96 of these subjects have been previously published (1). Volunteers were young (mean age, 25.5  $\pm$  3.0 yr) and predominantly female (75%). All Peace Corps volunteers were authorized to receive a follow-up evaluation by an endocrinologist after returning from Niger. Some follow-up evaluations were incomplete, as some of the subjects chose not to visit an endocrinologist upon returning, and different endocrinologists obtained different follow-up laboratory studies. The cumulative total dose of iodine ingested by each volunteer could not be determined, as iodine consumption varied depending on length of stay in Niger, the frequency of water filter changes, and the amount of water consumed.

### Assessment of goiter

The presence or absence of goiter was assessed by palpation by two physicians before correction of the iodine excess. Goiter size was graded per WHO recommendations (3); the least severe classification was assigned in the five cases where observers disagreed. The presence or absence of goiter was evaluated again an average of 30 wk after correction of the iodine excess. Ultrasound evaluation was not performed.

### Laboratory studies

Serum TSH,  $T_4$ , and free  $T_4$  levels were determined by chemiluminescence immunometric assays (performed by Quest Laboratories, Teterboro, NJ). Normal ranges were as follows: TSH, 0.40–4.20 mU/

Abbreviations: TPO, Thyroid peroxidase.

liter;  $T_4$ , 58–154 nmol/liter (4.50–12.0  $\mu\text{g}/\text{dl}$ ); and free  $T_4$ , 22.5–49 pmol/liter (1.75–3.80 ng/dl). TPO antibody levels were measured by ELISA (American Laboratory Products Co., Ltd., Lindham, NH), with normal values below 20,000 IU/liter (<20 IU/ml). Total serum iodine concentrations (normal range, 45–100  $\mu\text{g}/\text{liter}$ ) were measured spectrophotometrically by a modification of the method of Benotti *et al.* (4). Thyroid function tests and serum iodine concentrations were carried out upon completion of the study in most, but not all, subjects.

### Statistical analysis

Most quantitative data were compared using paired sample *t* tests. A signed-rank test was used to determine differences between TSH values during and after excess iodine exposure. McNemar's paired sample  $\chi^2$  test was used to compare the presence or absence of goiter during and after excess iodine exposure. A  $\chi^2$  test was used to assess associations between elevated TPO antibody levels and goiter and between elevated TPO antibody levels and elevated serum TSH values. Unless otherwise specified, data are presented as the mean  $\pm$  SD. All *P* values are two-tailed. Significance was indicated by *P* < 0.05.

## Results

### Goiter prevalence

Ninety-three of the 102 subjects had clinical thyroid evaluation both during and after excess iodine ingestion. Thyroid ultrasound was not performed. Goiter was present in 41 of the subjects (44%) during iodine ingestion, and prevalence apparently decreased to 28 of these 93 subjects (30%) after removal of excess iodine (*P* < 0.001; Table 1). However, thyroid palpation was performed by different examiners at the follow-up visit. No volunteers had overt symptoms of thyroid dysfunction as evaluated clinically.

### Serum iodine

Fifty-one of the 102 volunteers had total serum iodine levels measured during and after excess iodine exposure. Mean serum iodine decreased from  $293 \pm 306$  to  $84 \pm 46$   $\mu\text{g}/\text{liter}$  (*P* < 0.0001).

### Serum $T_4$ and free $T_4$

Eighty-eight of the 102 volunteers had total serum  $T_4$  values measured during and after excess iodine exposure. Mean total serum  $T_4$  values increased from  $100.4 \pm 20.6$  nmol/liter ( $7.8 \pm 1.6$   $\mu\text{g}/\text{dl}$ ) to  $113.3 \pm 24.5$  nmol/liter ( $8.8 \pm 1.9$   $\mu\text{g}/\text{dl}$ ; *P* = 0.002). Eighty-seven of the volunteers had serum free  $T_4$  values measured during and after excess iodine ingestion. Serum free  $T_4$  increased from a mean of  $32.2 \pm 6.4$  pmol/liter ( $2.5 \pm 0.5$  ng/dl) to  $34.7 \pm 6.4$  pmol/liter ( $2.7 \pm 0.5$  ng/dl; *P* = 0.01).

### Serum TSH

Ninety of the volunteers had serum TSH values measured before and after excess iodine ingestion. During iodine ingestion the geometric mean for serum TSH values was 2.63 mU/liter, which significantly decreased after removal of the excess iodine to 1.07 mU/liter (*P* < 0.0001). Serum TSH was greater than 4.2 mU/liter in 29% of 100 volunteers during iodine ingestion, which decreased to 5% of the 90 volunteers after removal of the excess iodine. Serum TSH values were less than 0.4 mU/liter in 5 of 90 volunteers (6%) during iodine ingestion and in 13 of 90 (14%) after removal of excess iodine (*P* < 0.05). Serum TSH values were suppressed below the limits of the assay (<0.02 mU/liter) in only a single subject during excess iodine ingestion; that subject had a TPO antibody level of 5700 IU/liter (5.7 IU/ml), serum iodine level of 255  $\mu\text{g}/\text{liter}$ , and no goiter. That subject's TSH had normalized to 1.97 at a 16 wk follow-up exam. It is unknown whether any treatment for a thyroid condition occurred in the interval between exams. TSH levels were also suppressed in a second subject 25 wk after removal of excess iodine. That subject had an initial TSH value of 1.7 mU/liter, an initial anti-TPO antibody level of 1900 IU/liter (1.9 IU/ml), and an initial serum iodine level of 180  $\mu\text{g}/\text{liter}$ . A goiter was present at both the initial and follow-up exams. No follow-up anti-TPO antibody level was obtained, and further clinical information about this subject was unavailable.

### Serum TPO antibodies

Serum TPO antibodies were above 20,000 IU/liter (>20 IU/ml) in 14 of 100 volunteers (14%) during excess iodine ingestion. TPO antibody values greater than 20,000 IU/liter were not significantly associated with the presence of goiter (*P* = 0.75) or with serum TSH levels of more than 5 mU/liter (*P* = 0.55). Fifty-two of those volunteers had follow-up TPO antibody measurements, and of those, only 4 (8%) had antibody levels greater than 20,000 IU/liter. When the mean TPO antibody values during and after iodine ingestion were compared in those 52 volunteers, there was a significant decrease from  $32,800 \pm 128,900$  to  $21,900 \pm 104,700$  IU/liter (*P* < 0.01). The groups with and without follow-up TPO antibody measurements appeared to be relatively similar, with 7 of 52 subjects (13%) in the group with follow-up values and 7 of 48 subjects (15%) in the group without follow-up TPO antibody levels having initial TPO antibody values greater than 20,000 IU/liter.

**TABLE 1.** Thyroid parameters during and after excess iodine exposure

	No. <sup>a</sup>	During excess iodine exposure	After excess iodine exposure <sup>b</sup>
TSH (geometric mean, mU/liter)	90	23.6	1.07
Anti-TPO antibody (mean $\pm$ SD, IU/liter)	52	$0.033 \pm 0.13$	$0.022 \pm 0.10$
$T_4$ (mean $\pm$ SD, nmol/liter)	88	$100.4 \pm 20.6$	$113.3 \pm 24.5$
Free $T_4$ (mean $\pm$ SD, pmol/liter)	87	$32.2 \pm 6.4$	$34.7 \pm 6.4$
Goiter (n, %)	93	41 (44%)	28 (30%)

<sup>a</sup> Number of subjects for whom values were obtained both during and after excess iodine exposure.

<sup>b</sup> All differences between values obtained during excess iodine exposure and those obtained after excess iodine exposure were significant at the *P* < 0.05 level.

## Discussion

Previously published reports have described both subclinical and overt thyroid dysfunction as a result of excess iodine ingestion. Goiter, hypothyroidism, and/or a rise in serum TSH values have been reported to result from ingestion of excess iodine in medications such as amiodarone (5), as a natural contaminant of drinking water (6), as a byproduct of iodine-containing water purification systems (7–10), in iodine-containing mouth rinses (11), and in the diet (seaweed ingestion) (12). Individuals with underlying autoimmune thyroid disease, those with a previous history of postpartum thyroiditis or subacute thyroiditis, or patients who have undergone partial thyroidectomy have all been shown to be prone to iodine-induced goiter and hypothyroidism (13). Additionally, although the natural history of thyroid dysfunction related to acute excess iodine ingestion has been well characterized, the effects of chronic iodine excess remain poorly understood.

Acute excess iodine ingestion has long been known to result in a transient decrease in iodine organification, termed the acute Wolff-Chaikoff effect (14). With sustained excess iodine exposure, however, most individuals' thyroid glands escape from this acute Wolff-Chaikoff effect despite continued excess iodine exposure and resume synthesis of normal amounts of  $T_4$  and  $T_3$ . The mechanism responsible for this escape or adaptation to the iodine load probably involves a decrease in the  $Na^+/I^-$  symporter protein, resulting in a decrease in thyroid iodide content (15). In some individuals this escape phenomenon does not occur, and those patients develop iodine-induced hypothyroidism. Such hypothyroidism generally is reversible when the source of excess iodine exposure is removed.

In this study inadvertent excess iodine ingestion from the water purification system by Peace Corps volunteers in Niger for up to 32 months between 1995 and 1998 resulted in a variety of thyroid abnormalities. During the prolonged excess iodine exposure there were marked increases in serum total iodine concentrations, and the prevalence of goiter, elevated serum TSH values, and elevated serum TPO antibody values increased. The prevalence of all abnormalities decreased after removal of excess iodine from the drinking water system.

There was a high prevalence of goiter among Peace Corps volunteers in this study at baseline in both euthyroid and hypothyroid individuals. Although an increase in thyroid size in the presence of excess iodine ingestion has been noted previously (16, 17), the mechanism for goiter formation remains unclear. It has been suggested that an increase in lymphoid infiltration or a mild chronic rise in TSH may be responsible. In one histological study of the thyroid glands of 28 Japanese patients chronically exposed to excess dietary iodine, 13 had lymphocytic infiltration, and 25 had moderate to marked follicular hyperplasia (12).

Although individuals with underlying autoimmune thyroid disease are more likely to develop complications of excess iodine ingestion, it is unclear whether excess iodine ingestion itself can lead to autoimmune disease. Animal studies have suggested that excess iodine exposure predisposes to the development of autoimmune thyroid disease

(18). However, controversy exists about whether there is a relationship between excess iodine ingestion and the development of Hashimoto's thyroiditis in humans (19). It has been observed that in areas of Japan where dietary iodine intake is high, the incidence of Hashimoto's thyroiditis is higher than in areas of low to normal dietary iodine intake (20). An increase in lymphocytic infiltration often occurs after iodine repletion in iodine-deficient regions (21). However, other studies have failed to show a relationship between increased iodine intake and autoimmunity (22, 23). In this study some Peace Corps volunteers had anti-TPO antibodies during excess iodine exposure. These abnormal TPO antibody titers decreased in some, but not all, subjects when excess iodine was eliminated. This suggests that excess iodine ingestion may induce thyroid autoimmunity in an otherwise healthy young population.

The findings in this study have significant public health implications. In 1998, an estimated 60,000 iodine resin devices and 300,000 bottles of iodine tablets were sold to U.S. civilians for water disinfection (24). In addition, iodine-based water purification systems are routinely used by the military, in international relief efforts, and by other government-sponsored programs. In this regard we have recently reported that excess iodine ingestion by American astronauts from water treated with iodine for purification in space resulted in a small transient rise in serum TSH values upon return to earth (25). Since 1998, the iodine has been removed from astronauts' potable water by an anion exchange resin just before the water is consumed, and no rise in serum TSH values has been observed. It is probably inadvisable for pregnant women, individuals with a history or a strong family history of thyroid disease, especially autoimmune thyroid disease, or individuals residing in areas of endemic iodine deficiency to use iodine-based methods of water purification unless extremely careful monitoring of the iodine content is carried out. Any individual anticipating prolonged ingestion of excess amounts of iodine in medications or as a byproduct of a water purification system should see a physician for a baseline physical exam to exclude the presence of preexisting goiter and to measure thyroid function tests and serum thyroid antibody levels to rule out abnormalities. Repeat thyroid function tests should then be repeated at intervals until excess iodine ingestion is eliminated.

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