

CLINICAL STUDY

Thyroid and the environment: exposure to excessive nutritional iodine increases the prevalence of thyroid disorders in São Paulo, Brazil

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Abstract

Objective: To evaluate the prevalence of chronic autoimmune thyroiditis (CAT) and iodine-induced hypothyroidism, hyperthyroidism (overt and subclinical), and goiter in a population exposed to excessive iodine intake for 5 years (table salt iodine concentrations: 40–100 mg/kg salt).

Design: This was a population-based, cross-sectional study with 1085 participants randomly selected from a metropolitan area in São Paulo, Brazil, and conducted during the first semester of 2004.

Methods: Thyroid ultrasound examination was performed in all participants and samples of urine and blood were collected from each subject. Serum levels of thyroid-stimulating hormone, free thyroxine, and anti-thyroid peroxidase (TPO) antibodies, urinary iodine concentration, thyroid volume, and thyroid echogenicity were evaluated. We also analyzed table salt iodine concentrations.

Results: At the time the study was conducted, table salt iodine concentrations were within the new official limits (20–60 mg/kg salt). Nevertheless, in 45.6% of the participants, urinary iodine excretion was excessive (above 300 µg/l) and, in 14.1%, it was higher than 400 µg/l. The prevalence of CAT (including atrophic thyroiditis) was 16.9% (183/1085), women were more affected than men (21.5 vs 9.1% respectively, $P=0.02$). Hypothyroidism was detected in 8.0% (87/1085) of the population with CAT. Hyperthyroidism was diagnosed in 3.3% of the individuals (36/1085) and goiter was identified in 3.1% (34/1085).

Conclusions: Five years of excessive iodine intake by the Brazilian population may have increased the prevalence of CAT and hypothyroidism in subjects genetically predisposed to thyroid autoimmune diseases. Appropriate screening for early detection of thyroid dysfunction may be considered during excessive nutritional iodine intake.

European Journal of Endocrinology 159 293–299

Introduction

Prevalence rates of thyroid dysfunction vary around the world according to the studies from different countries (1–6). These differences may be due to variations in disease definition, heterogeneity of the studied populations, relative insensitivity of thyroid function measurements, and absence of ultrasound imaging of the thyroid gland (2–5). In the Wickham survey, 7.5% of women and 2.8% of men of all ages had hypothyroidism as defined by serum thyroid-stimulating hormone (TSH) level above 6 mU/l (2). After reviewing their data 20 years later and comparing with 12 similar studies from different countries, Vanderpump *et al.* (3) concluded that primary thyroid failure has a prevalence of about 5% in multiple populations. In a very large population-based study ($n=25\,862$), Canaris *et al.* (4) observed elevated serum TSH levels in 9.5% of the participants. Virtually all

studies report higher prevalence rates of hypothyroidism in women and in advanced age (4–8).

Nutritional iodine status is an important factor associated with thyroid dysfunction and thyroid autoimmunity (9). As indicated by the World Health Organization, more than two-thirds of the 5 billion people living in countries affected by iodine deficiency now have access to iodized salt (10). In South America, iodine nutrition has improved considerably over the last decade; however, excessive iodine intake has been confirmed in Brazil and Chile, where urinary iodine excretion concentrations above 300 and 500 µg/l respectively have been demonstrated (11). Excessive dietary iodine is associated with increased risk for chronic autoimmune thyroiditis (CAT), hypothyroidism (mostly in women), and hyperthyroidism (mostly in elderly individuals) (12–17). Some studies have indicated that excessive iodine intake may increase thyroid

volume in children (18) and increase the risk of *post partum* thyroiditis (19).

In Brazil, a national survey conducted in 1994 detected a relatively low iodine intake (median urinary iodine excretion <100 µg/l) in more than 50% of 20 000 schoolchildren evaluated (20, 21). As a consequence, the Brazilian health authorities increased the iodination of table salt from 40–60 mg iodine per kilogram of salt to 40–100 mg/kg in 1998. Two population studies conducted after the iodine fortification (11, 22) documented that more than 60% of the examined subjects had elevated median urinary iodine excretion (>300 µg/l), indicating that the Brazilian population became exposed to excessive iodine from 1998 to 2003, after which iodination of table salt was lowered to 20–60 mg/kg of salt.

In this study, we aimed to evaluate the consequences to the thyroid gland of 5 years of excessive nutritional iodine intake in Brazil (1998–2003) in a cohort of randomly selected individuals from the metropolitan region of São Paulo. We examined all participants with thyroid ultrasound, serum-free thyroxine (T₄) and TSH, presence of anti-TPO antibodies, and urinary iodine excretion, as well as tested the iodine content of the table salt being used by the participants at the time the evaluation was conducted.

Subjects and methods

Subjects

This was a population-based, cross-sectional study with participants randomly selected from a metropolitan area in São Paulo, Brazil and conducted during the first semester of 2004. To select the target districts to be assessed, a detailed map of two urban areas with single-family homes was obtained and blocks were selected by chance. From these, streets were arbitrarily chosen and houses within the streets were randomly selected. Each home was visited by two medical students and one or more residents were randomly chosen and questioned whether he/she would be willing to participate in the study. The interviews were conducted by the medical students and the visits took place on Fridays and

Saturdays. As expected, the sample included more women, since men are less likely to be home during workdays. Also, most men enrolled were older than 30 years, since young men are less likely to be home on Saturdays. As a consequence, women outnumbered men in the age groups below 50 years (Table 1).

During the visit, an oral questionnaire was administered to each participant eliciting personal information and data on the economic status of the family, eating habits, brand name of the table salt used, and estimation of the amount of salt ingested per day. Eight patients were on LT4 treatment for more than 5 years, all of them with the diagnosis of atrophic autoimmune thyroiditis. For the remaining eight patients with atrophic thyroiditis, the information obtained was that they were on and off LT4 substitutive therapy for more than 5 years. All these patients had elevated serum TSH concentrations (mean ± s.d. 11.73 ± 7.8 mU/l). Pregnant and lactating women were not included in the study. Sixteen patients with overt (n=7) and subclinical hypothyroidism (n=9) were excluded because in the past they have been submitted to either thyroid surgery (n=5) or radioiodine therapy (n=9). All participants were evaluated with thyroid B-mode ultrasound by the same observers (RAYC and EKT) using a portable General Electric (GE) apparatus with a 7.5 mHz probe. The samples of urine and blood were obtained from each subject and kept refrigerated until analysis.

The Cochran formula ($n=pq/(d/t)^2$) (23) was used to determine the sample size based on the estimated population of São Paulo City (11 million inhabitants). The application of this formula yielded n=385, whereas data were collected on 1085 subjects (Table 1).

All participants signed a detailed consent form. The study was approved by the Ethical Committee for Research Projects of the Hospital das Clinicas, University of São Paulo Medical School.

Methods

Serum levels of TSH, free T₄, and anti-TPO antibodies (normal <35 U/ml) were assayed by chemiluminescence (Elecsys, Roche Diagnostics). The reference range for normal TSH and free T₄ values was derived from 320 subjects from the study. These individuals had no history

Table 1 Distribution of subjects by gender and age groups.

Age group (years)	Female (F)		Male (M)		Ratio M:F
	n (%)	Mean age (years)	n (%)	Mean age (years)	
<30	113 (16.7)	24.7	16 (3.9)	24.1	1:7.0
30–39	122 (18.0)	34.8	27 (6.6)	35.4	1:4.5
40–49	184 (27.1)	44.5	68 (16.7)	46.1	1:2.7
50–59	138 (20.4)	53.6	129 (31.7)	54.4	1:1.0
60–69	88 (13.0)	64.0	109 (26.8)	63.8	1:0.8
70–79	28 (4.1)	72.7	51 (12.5)	72.5	1:0.5
>80	5 (0.7)	81.0	7 (1.7)	82.0	1:0.7
Total	678	45.3	407	55.8	1:1.67

of thyroid disease, negative antithyroid antibodies, normal thyroid gland on ultrasound (normal volume, echogenicity, and absence of cysts and nodules), and urinary iodine excretion between 100 and 299 $\mu\text{g/l}$. Results were considered to be within the normal range if situated between the 2.5th and 97.5th percentile of this normal population. In this reference cohort, serum TSH levels ranged from 0.6 to 3.7 mU/l and serum free T_4 from 0.87 to 1.6 ng/dl. Thyroid volume ranged from 6 to 14.2 ml (women) and from 7 to 14.9 ml (men) and was consistent with normal range for the city of São Paulo, as previously described (8, 22).

Urinary iodine excretion was determined by the colorimetric ceric arsenite method, based on the Sandell–Kolthoff reaction, as previously described (21). Normal reference range was considered 100–299 $\mu\text{g/l}$, according to the World Health Organization (10).

On ultrasound evaluation, the echogenicity of the thyroid was graded by comparison with the echogenicity of the neck muscles and defined as normal (grade 1), mildly hypoechoic (grade 2), moderately hypoechoic (grade 3), and markedly hypoechoic (grade 4). Thyroid volume was estimated by ultrasound in all participants. The volume of each lobe was calculated by the formula longitudinal diameter \times transversal axis \times anteroposterior axis multiplied by 0.52. The total volume of the thyroid was the sum of both lobes plus the volume of the isthmus, calculated as width \times height \times length \times 0.52 (8, 22). Goiter was defined by ultrasound as a thyroid volume greater than 16.0 ml for women and 18.1 ml for men.

Samples of the table salt in use by the family at the time of the visit were collected in plastic bags and analyzed for iodine content at the Public Health Reference Laboratory, São Paulo, Brazil.

Diagnostic criteria for thyroid disease

CAT was diagnosed when anti-TPO antibodies were positive (>35 U/ml) and grade 3 or 4 thyroid hypoechogenicity was concurred by both observers on ultrasound evaluation. The presence of low titer of anti-TPO antibodies (between 36 and 100 U/ml) without ultrasound documented hypoechogenicity may be found in healthy subjects without evidence of thyroid disease (1, 26). Therefore, these individuals were not included as affected by CAT. The diagnosis of atrophic autoimmune thyroiditis was established in patients with reduced thyroid volume on ultrasound (<5 ml) regardless of anti-TPO antibody status. These patients were then included in the CAT group and considered as the end stage of the autoimmune process with destruction of the affected thyroid gland (1). Overt hypothyroidism was diagnosed in subjects with serum TSH above 4.1 mU/l and free T_4 levels below 0.9 ng/dl; subclinical hypothyroidism was determined to be present when TSH levels were above 4.1 mU/l but free T_4 levels were within the normal range. Both modalities of decreased thyroid function were within the group of CAT.

Overt hyperthyroidism (low or undetectable TSH and high free T_4 levels) and subclinical hyperthyroidism (low or undetectable TSH and normal free T_4 levels) were diagnosed irrespective of thyroid ultrasound features.

Statistical analysis

Pearson's χ^2 - and Fisher's exact tests were used to compare categorical values. For some analyses, the fitting linear models and characteristics (slope, R^2 , and P value) were applied. The parametric Student's t -test was used to compare different levels of urinary iodine excretion with gender. The locally weighted polynomial regression (Lowess, no parametric) was applied to evaluate the association between thyroid volume and age; the absence of association between these two variables was later confirmed by log transformation. All statistical analyses were performed at a significance level of 0.05 with R software, version 2.5.0 (24).

Results

Subjects

Table 1 summarizes the main characteristics of the population analyzed. A total of 1085 individuals between the ages of 20 and 87 years were evaluated. From these, 678 were women (62.5%, mean age \pm s.d. 45.3 ± 14.0 years) and 407 were men (37.5%, 55.8 ± 12.0 years; ratio men/women 1:1.67).

Urinary iodine excretion

The distribution of urinary iodine excretion in the studied population is shown in Fig. 1. Fasting urine

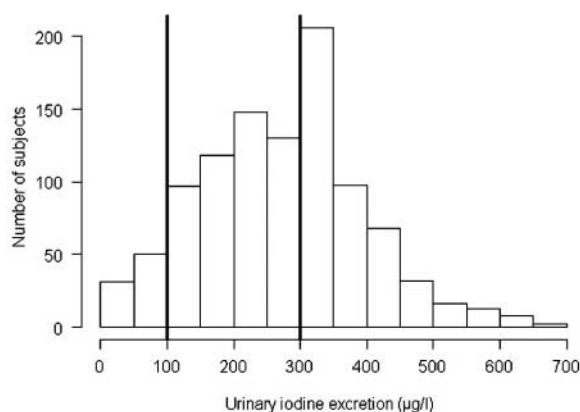


Figure 1 Distribution of urinary iodine excretion in the studied population. Note that 7.8% of all subjects had low urinary iodine excretion (≤ 100 $\mu\text{g/l}$), whereas an elevated excretion (>300 $\mu\text{g/l}$) was observed in 45.1% of the samples. Moreover, 11% of the women and 17% of the men had values above 400 $\mu\text{g/l}$. Men had a significantly higher excretion of median urinary iodine (women = 270 $\mu\text{g/l}$ and men = 290 $\mu\text{g/l}$; $P=0.028$, Fisher's exact test). Vertical lines indicate the normal range.

specimens suitable for iodine content analysis were obtained in 1022 participants and kept refrigerated until assayed. The total cohort median urinary iodine excretion was 273 µg/l (women=270 µg/l and men=290 µg/l). Men had a significant higher excretion of iodine when compared with women ($P=0.028$, Fisher's exact test). Normal urinary iodine excretion (100–299 µg/l) was present in 49.6% of the women and 43.0% of the men. A relatively low urinary iodine excretion (<100 µg/l) was detected in 8.11% of the women and 7.3% of the men, whereas an elevated excretion was observed in 461 (45.1%) subjects (women=42.3% and men=49.6%; $P=0.02$). Five participants excreted more than 1000 µg/l and were considered to have possible exogenous iodine contamination.

Table salt iodine content

Samples of the table salt being consumed in the home at the moment of the visit had a mean \pm s.d. concentration of iodine of 35.6 \pm 8.9 mg/kg of salt (range 23.8–81.2 mg/kg). Three samples were above the legal limit of 60 mg/kg and none had less than 20 mg/kg.

Thyroid ultrasound

Twenty-three women (3.4%) and three men (0.73%) had atrophic thyroid gland ($P=0.004$, Fisher's exact test); 14 women and 2 men had an atrophic thyroid associated with positive anti-TPO antibodies. An enlarged and frequently nodular goiter was present in 34 patients (Table 2); from these, 24 were women (3.54%) and 10 were men (2.46%). A significant increase in thyroid volume with advancing age was not observed in both genders.

Prevalence of CAT

The prevalence of thyroid disease in the studied population is presented in Table 2 and the prevalence distribution of CAT by age group in women and men is shown in Fig. 2. Ten subjects (eight women and two men)

had low (36–100 U/ml) positive anti-TPO antibodies but normal thyroid ultrasound (echogenicity and volume), so were not considered to have CAT. The overall prevalence of CAT (including atrophic thyroiditis) was 16.87%; it significantly affected more women (21.53%) than men (9.09%; $P=0.02$). Women younger than 30 years had a lower prevalence of CAT when compared with women between 60 and 69 years (16.81 and 28.41% respectively), whereas older men (between 50 and 59 years) had a higher prevalence (11.64%) when compared with younger men (between 30 and 39 years, 7.40%). There was a significant increase in the prevalence of CAT with advanced age in both genders ($r^2=0.745$, $P=0.0269$).

Most of the subjects with CAT were euthyroid (women 51.3% and men 56.7%). Women had a higher prevalence of CAT associated with overt hypothyroidism when compared with men (women 39/146 (26.7%) and men 6/37 (16.2%); $P<0.01$). CAT associated with subclinical hypothyroidism was detected in 18/146 (12.3%) of the women and in 8/37 (21.6%) of the men. Atrophic thyroiditis was identified in 14/183 (9.6%) of women and in 2/37 (5.4%) of men with CAT, being considered as the end stage of the destructive autoimmune process.

Prevalence of hyperthyroidism

The prevalence of hyperthyroidism in the studied population in relation to gender and age is shown in Fig. 3. Hyperthyroidism was detected in 3.32% of subjects. From these, 1.66% had overt hyperthyroidism and 1.66% had subclinical hyperthyroidism. Subclinical hyperthyroidism was more prevalent in women (2.06%) than men (0.98%), although it did not attain statistical significance (Table 2). In women (but not in men), both subclinical and overt hyperthyroidism were more prevalent with advancing age. The high relative prevalence of hyperthyroidism in men aged 70–79 years old may be related to the low number of patients included in this group (Fig. 3).

Table 2 Prevalence of thyroid disease in the studied population.

Thyroid disease	Total population (1085) <i>n</i> (%)	Women (678) <i>n</i> (%)	Men (407) <i>n</i> (%)	<i>P</i>
Chronic autoimmune thyroiditis ^a	183 (16.87)	146 (21.53)	37 (9.09)	<0.001
Euthyroidism	96 (8.85)	75 (11.10)	21 (5.16)	<0.001
Overt hypothyroidism	45 (4.15)	39 (5.75)	6 (1.47)	<0.001
Sub-clinical hypothyroidism	26 (2.39)	18 (2.65)	8 (1.96)	NS
Atrophic thyroiditis	16 (1.47)	14 (2.06)	2 (0.49)	<0.01
Hyperthyroidism	36 (3.32)	26 (3.83)	10 (2.46)	NS
Overt	18 (1.66)	12 (1.77)	6 (1.47)	NS
Sub-clinical	18 (1.66)	14 (2.06)	4 (0.98)	NS
Goiter	34 (3.13)	24 (3.54)	10 (2.46)	NS

^aIncluding patients with atrophic thyroiditis.

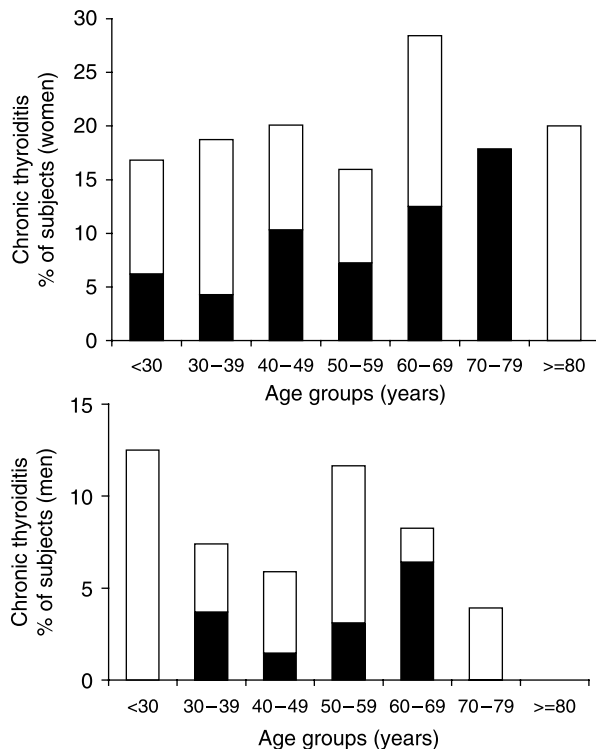


Figure 2 Prevalence distribution of chronic autoimmune thyroiditis by age in women and men. Bars indicate the percentile of chronic autoimmune thyroiditis. Black bars indicate the percentile of patients with chronic autoimmune thyroiditis associated with overt or subclinical hypothyroidism in women (upper panel) and men (lower panel). Note that there was a significant increase of hypothyroidism in both genders with advancing age ($r^2=0.745$, $P=0.02$).

Discussion

The influence of dietary iodine on thyroid function has been clearly shown in several studies with experimental autoimmune thyroiditis (1). This association may be due to an iodine-induced increase in the immunogenicity of the thyroglobulin molecule (and possibly other thyroid antigens as well) attracting antithyroid antibodies and culminating in thyroid injury (9, 25). High iodine intake has been shown to initiate and exacerbate thyroid infiltration by lymphocytes in genetically susceptible BB/W rats (26). In humans, susceptibility to autoimmune thyroid disease (AITD) clearly increases with age, as a result of extended exposure to environmental factors (such as excessive nutritional iodine intake) and changes in immunoregulation. The identification of genes placing individuals at an increased risk for development of AITD has been a slow process. However, as recently reviewed by Zeitlin *et al.* (27), novel insights have been made. AITD runs in families and more than 50% of patients with AITD have a familiar history suggesting that genetically predisposed individuals under a specific environment condition (iodine excess) may develop AITD.

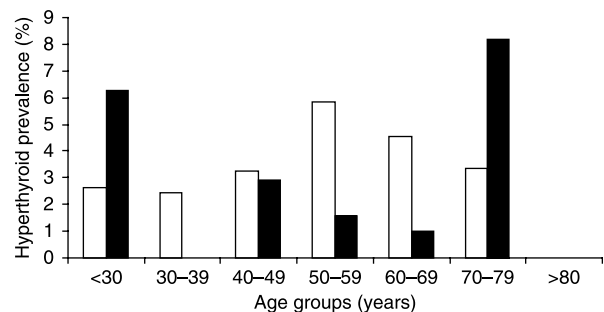


Figure 3 Prevalence of hyperthyroidism in the studied population in relation to gender and age. Note that hyperthyroidism was more frequent in women (white bars) with advancing age (but not in men, black bars). The high relative prevalence of hyperthyroidism in men aged 70–79 years may be related to the low number of patients respectively included in this group.

In many countries, the introduction of iodine prophylaxis has increased the prevalence of CAT and induced a surge in thyroid antibodies positivity (12, 16). Zois *et al.* (28) have reported the impact of increased nutritional iodine in 3000 schoolchildren in Northern Greece. After 7 years of iodine prophylaxis, 10% of the children had ultrasonographic features of CAT associated with positive anti-TPO antibodies, whereas 2.5% had laboratory evidence of subclinical hypothyroidism. In a recent study by Teng *et al.* (29) conducted in three areas of China with different levels of iodine intake (low, median urinary iodine excretion = 84 µg/l; more than adequate, 243 µg/l; and excessive, 651 µg/l), the authors demonstrated that patients from the area with excessive iodine intake had 5.6 times more CAT and 6.6 times more hypothyroidism (subclinical and overt) when compared with patients from the area with low iodine intake. The authors concluded that excessive iodine intake may lead to autoimmune thyroiditis and hypothyroidism.

In the same year of the Brazilian population-based survey of 1994 that found a relatively low iodine intake in a large number of examined schoolchildren (20), Tomimori *et al.* (8) examined 547 healthy overweight subjects in São Paulo, Brazil, with thyroid ultrasound, thyroid function tests, and anti-TPO antibody measurements. The authors found in this largely urban population, a prevalence of CAT of 9.4% and clinical and laboratory evidence of hypothyroidism in 4.9%. The median urinary iodine excretion in this population was 106 µg/l.

In 1995, following the approval of a legislation that regulated iodine in a concentration of 40–100 mg/kg of salt for human use, it was believed that iodine deficiency and its consequences would be abolished in Brazil. When our group launched the Thyromobil Project in 2001 (11), examining 2013 schoolchildren in 21 villages of 8 Brazilian states, the initial conclusion was that goiter had been practically eliminated. However, 67% of the schoolchildren were found to have a urinary iodine excretion > 300 µg/l and 35% of them excreted

more than 500 µg iodine per liter of urine, compatible with excessive iodine intake mainly, if not exclusively, from iodized table salt. Therefore, the recommended table salt iodination was reduced to 20–60 mg/kg salt in 2004.

In any event, it became clear that for almost 5 years the Brazilian population had been exposed to excessive iodine intake. As a consequence, and as observed in the present study, there was a significant increase in the prevalence of CAT from 9.4 (8) to 16.9% in the metropolitan area of São Paulo. Although the prevalence of 9.4% found by Tomimori *et al.* (8) among healthy overweight individuals may not represent the general population, the prevalence of CAT virtually doubled after 5 years of excessive iodine nutrition. Based on these observations, we strongly believe that the increase in prevalence of CAT (diagnosed by both positive anti-TPO antibodies and thyroid hypoechogenicity) presented in this study is associated with the increased iodination of table salt observed between 1998 and 2003.

Excessive iodine intake, as indicated by urine iodine excretion higher than 500 µg/l, has been also associated with increased thyroid volume (18). In our patients, thyroid volume was considered to be within the normal range for both genders, with an acceptable prevalence of nodular goiters of about 3% of the population.

A number of recent studies (30–32) have indicated that thyroid hypoechogenicity associated with positive anti-TPO antibodies is highly indicative of the presence of CAT. Raber *et al.* (30), using an arbitrary scale to define hypoechogenicity, have concluded that a markedly hypoechogenic thyroid gland has a positive predictive value for detecting autoimmune thyroiditis of 94% independent of the degree of hypothyroidism. Others (31) have introduced a quantitative gray-scale analysis of thyroid echogenicity for patients with Hashimoto's thyroiditis, showing that hypoechogenicity is significantly correlated with high serum TSH value and with the presence of anti-TPO antibodies. In this study regarding the thyroid hormone state, 96/183 (52.5%) of the subjects with CAT were euthyroid, whereas as expected overt hypothyroidism was significantly more frequent in women than in men.

It has been reported that a sudden increase in iodine supplementation increases the prevalence of hyperthyroidism (33). Our findings did not confirm this observation; however, it is possible that iodine-induced hyperthyroidism may have peaked in the years of excessive salt iodination (between 1998 and 2003). The absolute and relative prevalence rates of hyperthyroidism that we found in this study were higher than those observed in population studies conducted in other countries (4, 6, 7), but similar to the prevalence of hyperthyroidism (both overt and subclinical) in the 'more than adequate' and 'excessive' intake cohorts in China (29, 34). Therefore, we could not reach a

conclusion if there were a relationship between excessive iodine intake and increased prevalence of (overt and subclinical) hyperthyroidism.

In conclusion, there is no doubt that iodine supplementation should be instituted in countries like Brazil with history of chronic iodine deficiency dating back to the 19th century (21, 22). Nutritional iodine, however, should be maintained at safe levels. Excessive iodine intake (urinary iodine excretion > 300 µg/l) does not appear to be safe, especially for individuals with genetic potential to develop autoimmune disorders. Prolonged excessive iodine intake could eventually lead to a steep increase in CAT prevalence with resulting (subclinical and overt) hypothyroidism that could be not detected and treated accordingly. As demonstrated in this study, a large proportion of the Brazilian population may have unknowingly developed thyroid dysfunction when exposed to iodine excess. This evidence strongly supports appropriate screening for early detection of thyroid dysfunction in the presence of excessive iodine supplementation.

Acknowledgements

This study was made possible through a Research Grant (FAPESP 03/00827-0) from the State of São Paulo Research Foundation and a partial financial grant from Instituto da Tireoide. We gratefully acknowledge the major contribution in the field studies that was made by Thiago Ueda and Ana Carulina Lassa Moreno, both medical students from the University of São Paulo Medical School. We also acknowledge the laboratorial work of Maria Silvia Cardia and the statistical analysis by Elier Broche Cristo. We are grateful to the Health Authorities, nurses and social workers of the urban areas of São Paulo that were screened for thyroid diseases.

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Received 10 June 2008

Accepted 14 June 2008