Iodine Contributes to Thyroid Autoimmunity in Humans by Unmasking a Cryptic Epitope on Thyroglobulin

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Context: The mechanisms linking thyroid autoimmunity and iodine use in humans are unknown.

Objective: Our aim was to correlate iodine intake, thyroid autoimmunity, and recognition of thyroglobulin (Tg) epitopes after implementation of iodine prophylaxis.

Setting: The general community living in an Italian village was evaluated.

Main Outcome Measures: Thyroglobulin autoantibodies (TgAb), thyroperoxidase autoantibodies (TPOAb), and urinary iodine excretion were assessed in 906 iodized salt users (IS-users) and 389 nonusers (IS-nonusers). Ultrasound (US) was performed to identify thyroid hypoechogenicity, suggestive of Hashimoto thyroiditis (HT). TgAb epitope pattern in 16 IS-users and 17 IS-nonusers was evaluated by an inhibition binding assay to Tg, using human monoclonal TgAb-Fab directed to A, B, C, and D epitopes on Tg.

Results: Median urinary iodine excretion was slightly higher in IS-users than in IS-nonusers (112.0 μg/L vs 86.5 μg/L; $P < .01$). TgAb, and not TPOAb, was more frequent in IS-users (18.9% vs 13.6%, $P = .02$). HT-US was found in 87 subjects, among whom both positive TgAb (58.4% vs 31.8%, $P = .03$) and TPOAb (61.5% vs 45.4%. $P = .04$) were more frequent in IS-users. In this group significantly higher serum levels of TgAb (median 108 U/mL vs 30 U/mL; $P = .02$), but not of TPOAb, were present. Iodized salt use had no effect on the 1208 non HT-US subjects. TgAb directed to the epitope B of Tg were more frequent in IS-users than in IS-nonusers (27.5% vs 3.0%, $P = .047$).

Conclusions: Iodine-induced thyroid autoimmunity is related to TgAb and the unmasking of a cryptic epitope on Tg contributes to this relationship in humans. **(*J Clin Endocrinol Metab* 98: E1768–E1774, 2013)**

Iodine, a micronutrient of the diet, is an essential component of thyroid hormones. Iodine deficiency has several consequences on human health (reviewed in Refs. 1–4), referred to as iodine deficiency disorders (IDD), ranging from defective development of the central nervous system during the fetal-neonatal life, to goiter in the adult (reviewed in Ref. 2). Iodine prophylaxis through iodized salt, implemented by the World Health Organization and the International Council for the Control of Iodine Deficiency Disorders, has been shown not only to exert a pivotal role in abating IDD but also to modulate the pattern of thyroid diseases (5). Nevertheless, available evidence clearly confirms that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation (reviewed in Refs. 6, 7). Studies in populations living in areas with different iodine intake (reviewed in Refs. 8, 9) have shown a higher frequency of thyroid autoimmunity and hypothyroidism in iodine-replete than in iodine-defi-

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Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; HT, Hashimoto thyroiditis; IDD, iodine deficiency disorders; IQR, interquartile range; IS-users, iodized salt users; IS-nonusers, iodized salt nonusers; TAb, thyroid autoantibodies; Tg, thyroglobulin; TPOAb, thyroperoxidase autoantibodies; UIE, urinary iodine excretion; US, ultrasound.

cient populations. Accordingly, studies conducted in Denmark have also shown an increased incidence of thyroid autoantibodies (TAb) (10) and overt hypothyroidism (11) after the beginning of a cautious iodization program. The role of iodine in inducing thyroid autoimmunity is strongly supported by animal models. Excessive iodine intake can precipitate spontaneous thyroiditis in genetically predisposed animals, by increasing the immunogenicity of thyroglobulin (Tg) (12, 13, reviewed in Ref. 14).

The rise in urinary iodine excretion (UIE) that we observed in Pescopagano, an Italian village, 15 years after the introduction of iodine prophylaxis was associated with a reduction in the prevalence of goiter (particularly of nontoxic diffuse goiter), thyroid autonomy, and nonautoimmune hyperthyroidism and an increase of serum TAb and hypothyroidism, particularly of its subclinical form (15).

The aim of the present work was to confirm that in this population iodine intake is the main exogenous factor involved in thyroid autoimmunity and possibly to elucidate the mechanisms underlying this effect. As tools for the assessment of thyroid autoimmunity, we evaluated not only the positivity but also the level of serum TAb. Indeed, although low levels of TAb are not restricted to Hashimoto thyroiditis (HT), being also detectable in patients with goiter (16) or thyroid cancer (17, 18), as well as in subjects with no evidence of clinical thyroid disease (16), high titers of TAb are more closely associated with HT and hypothyroidism (19). We considered also the thyroid ultrasound (US) pattern for the diagnosis of HT. Indeed, full-blown HT is characterized by a nonhomogeneous, hypoechoic pattern at thyroid ultrasound (HT-US pattern), which is due to the reduced reflection of US beams caused by thyroid lymphocytic infiltration and scarring with loss of the follicular structure (20–22).

Our results suggest that iodine-induced thyroid autoimmunity correlates with Tg autoantibodies and that iodine exposes a cryptic epitope on Tg. We suggest that this is the mechanism involved in iodine-induced thyroid autoimmunity in humans.

Materials and Methods

Subjects

Examined were 1429 subjects, 1148 (80.3%) of which were actually residents in Pescopagano and 281 (19.7%) who came from the surrounding villages. Informed consent was obtained from parents of the minors and from adult subjects.

A questionnaire was completed including personal and family history of thyroid diseases. Alimentary habits and use of iodized salt were also evaluated. Of the 1429 subjects, 128 (8.9%) failed to answer this question or anamnestic data were not congruent within the same family and were excluded. As only six subjects had Graves disease, we excluded them from the analysis. Thus, clinical signs of thyroid autoimmunity were searched for in 1295 subjects (males, n = 502, females, n = 793, mean age ± SD = 45.7 ± 19.2 y). Nine hundred six (70.0%) declared to routinely use iodized salt (iodized salt users: IS-users) and 389 (30.0%) claimed to never use iodized salt (iodized salt nonusers: IS-nonusers).

Thyroid US

US was performed by two examiners (R.T. and A.L.) using a real-time instrument (Esaote; Biomedica) with a 7.5- to 10-MHz linear transducer. Thyroid echogenicity was evaluated in comparison with surrounding neck muscles by the examiners, who were not aware of clinical and laboratory data. Examiners evaluated thyroid pattern independently and discordant cases (about 10% of subjects) were re-examined; the assignment to one group was agreed. According to US pattern, the study population was subdivided into subjects with a hypoechoic pattern indicative of HT (HT-US, n = 87) and subjects with a normal or slightly hypoechoic US pattern (non-HT-US, n = 1208).

Laboratory evaluation

The number of urinary samples to analyze was determined according to the indications of the United Nations Children's Fund (23). According to this guideline, the sample size to analyze to assess iodine nutrition should be 385 subjects. We actually evaluated UIE in 468 urine samples (318 from IS-users and 150 from IS-nonusers) randomly selected of the 1295 subjects. UIE was measured by a colorimetric method using an autoanalyzer apparatus (Technicon), as already described (24) The results were calculated as micrograms of iodine per liter of urine.

TSH was determined by Immulite 2000 (Euro/DPC; normal values 0.4–3.6 μU/mL). Serum free thyroxine (FT4) and free triiodothyronine (FT3) were measured by a chemoluminescent assay (Vitros Ortho-Clinical Diagnostics; normal range FT4 7–17 pg/mL and FT3 2.7–5.7 pg/mL) (25).

Thyroglobulin autoantibodies (TgAb) and thyroperoxidase autoantibodies (TPOAb) were measured by an automated immunoassay system (AIA-Pack; Tosoh). TgAb and TPOAb were negative when $<$30 U/mL and $<$10 U/mL, respectively.

TgAb-Fab epitope pattern

The epitope pattern of TgAb was evaluated in 33 subjects (16 IS-users and 17 IS-nonusers) by inhibiting serum TgAb binding to Tg by recombinant human TgAb-Fab in ELISA. These sera had sufficiently high TgAb titers ($>$100 U/mL) to yield a significant ELISA signal that could be adequately inhibited by recombinant human TgAb-Fab in ELISA. Cloning and characterization of human recombinant monoclonal TgAb expressed as Fab have been previously described (26, 27). Four TgAb-Fab corresponding to four different epitope regions (A, B, C, and D) on Tg were used (27). The method has been previously described (18, 27, 28). Briefly, wells coated with human Tg (Calbiochem; 4 μg/mL, 4°C, overnight) were incubated with serial dilutions of sera with high levels of TgAb in the presence of each TgAb-Fab. TgAb binding was detected with antihuman IgG-Fc (Sigma Chemical Co.), which binds to IgG but not to Fab molecules. After the addition of substrate (*o*-phenylene diamine + H_2O_2) and H_2SO_4 to stop the reaction, the optical density was read at 490 nm. The inhibition by TgAb-Fab was calculated from the optical density values for serum TgAb alone − serum TgAb + TgAb-Fab and expressed as a percentage of serum TgAb alone.

Nonspecific binding of a TgAb-negative serum (6%–12%) was subtracted in calculating percentage inhibition. The experiments were performed three times, each time in triplicate.

Statistics

Results of UIE, serum levels of TgAb and TPOAb, and of inhibition by TgAb Fab are reported as median and interquartile range (IQR: 25th to 75th percentiles). Nonparametric tests (χ^2, Fischer exact test, Mann-Whitney *U* test) were used as appropriate and considered statistically significant when $P < .05$.

Results

Serum TAb and use of iodized salt

In agreement with the data collected through the questionnaire, UIE was significantly higher in IS-users (median 112.0 μg/L, IQR 65.0–166.0 μg/L) than in IS-nonusers (median 86.5 μg/L, IQR 48.0–132.0 μg/L; $P = .0006$).

Serum positivity of TAb (Figure 1), including TgAb and/or TPOAb, was more frequently observed in IS-users than in IS-nonusers (220/906, 24.3% vs 72/389, 18.5%, respectively, $\chi^2 = 5.2$, $P = .02$). In particular, the frequency of positive TgAb was significantly higher in IS-users than in IS-nonusers (171/906, 18.9% vs 53/389, 13.6%, in IS-users and IS-nonusers, respectively, $\chi^2 = 5.2$, $P = .02$), whereas serum TPOAb positivity, although higher in IS-users, was not significantly different between the two groups (153/906, 16.9% vs 51/389, 13.1%, $\chi^2 = 2.9$, $P = .09$).

HT and use of iodized salt

We considered the presence of hypothyroidism, a hypoechoic pattern at thyroid US (HT-US), and the positivity of serum TAb (positive serum TgAb and/or TPOAb) as clinical signs of HT. The frequency of hypothyroidism was not higher in IS-users compared to IS-nonusers (49/906, 5.4% vs 14/389, 3.6%; $\chi^2 = 1.9$, $P = .16$).

HT-US was found in 87/1295 (6.7%) and was strongly associated with circulating TAb. Indeed, the frequency of positive TAb (Table 1) was much higher in HT-US than in non-HT-US (59/87, 67.8% vs 233/1208, 19.3%, $\chi^2 = 109.4$, $P < .0001$) and this difference was statistically significant for both TgAb (45/87, 51.7% vs 179/1208, 14.8%, $\chi^2 = 77.2$, $P < .0001$) and TPOAb (55/87, 63.2% vs 149/1208, 12.3%, $\chi^2 = 158.3$, $P < .0001$). Furthermore, serum levels of both TgAb (median, IQR: 34 U/mL, 0–412 U/mL vs 0 U/mL, 0–7 U/mL; $P < .0001$) and TPOAb (142 U/mL, 0–566 U/mL, vs 0 U/mL, 0–0 U/mL; $P < .0001$) were significantly higher in HT-US than in non-HT-US (Table 1). Overall, the number of subjects with a high level of TAb (ie, TgAb and or TPOAb >100 U/mL) was significantly higher in HT-US than in non-HT-US (52/87, 59.8% vs 127/1208, 10.5%, $\chi^2 = 165.3$, $P < .0001$). These findings further confirm in this survey population that thyroid hypoechogenicity at US is closely associated with HT.

Similar to what was observed for hypothyroidism, the frequency of HT-US was also higher, even if not significantly different in IS-users compared to IS-nonusers (65/906, 7.2% vs 22/389, 5.7%; $\chi^2 = 1.0$, $P = .31$). In HT-US subjects the effect of iodine was particularly evident for TgAb (Figure 2). Indeed, 38/65 (58.4%) IS-users and only 7/22 (31.8%) IS-nonusers had positive TgAb ($\chi^2 = 4.7$, $P = .03$). For TPOAb this difference was also significant, but to a lesser extent (45/65, 69.2% vs 10/22, 45.4%, respectively, $\chi^2 = 4.0$, $P = .05$). In HT-US subjects, serum levels of TgAb were also significantly higher in IS-users

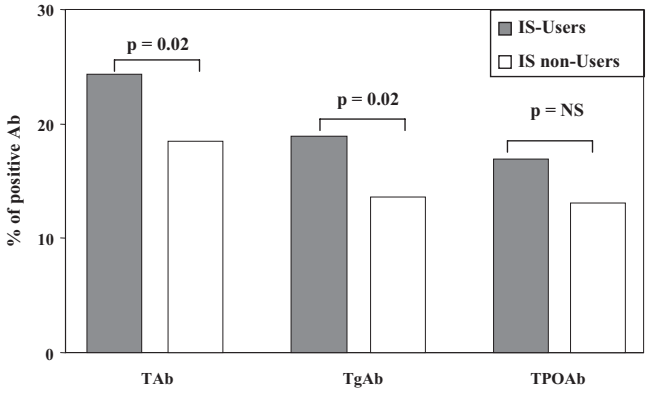

Figure 1. Frequencies of positive TAb, TgAb, and TPOAb according to the use of iodized salt (IS-users, *gray columns*, and IS-nonusers, *white columns*). The frequency of positive TAb and TgAb was significantly higher in IS-users than in IS-nonusers, whereas serum TPOAb positivity, although higher in IS-users, was not significantly different between the two groups (χ^2 *P* value reported).

Table 1. Relationship Between Serum Thyroid Autoantibodies and Hypoechoic Pattern at Thyroid Ultrasound

	HT-US (n = 87)	Non-HT-US (n = 1208)	*P*
Positive TgAb	45 (51.7%)	179 (14.8%)	<.0001[b]
Serum levels of TgAb, U/mL	34 (0–412)[a]	0 (0–7)[a]	<.0001[c]
Positive TPOAb	55 (63.2%)	145 (12.1%)	<.0001[b]
Serum levels of TPOAb, U/mL	142 (0–566)[a]	0 (0–0)[a]	<.0001[c]
Positive TAb	59 (67.8%)	233 (19.3%)	<.0001[b]
Positive high TAb	52 (59.8%)	127 (10.5%)	<.0001[b]

Abbreviations: non-HT-US, normal or slightly hypoechoic US pattern; positive TAb, positive TgAb and/or TPOAb; positive TgAb, serum level ≥30 U/mL; positive TPOAb, serum level ≥10 U/mL; positive high TAb, TgAb, and/or TPOAb >100 U/mL.

a Serum levels of TAb are expressed as median (IQR).

[b] χ^2 *P* value.

[c] Mann-Whitney *P* value.

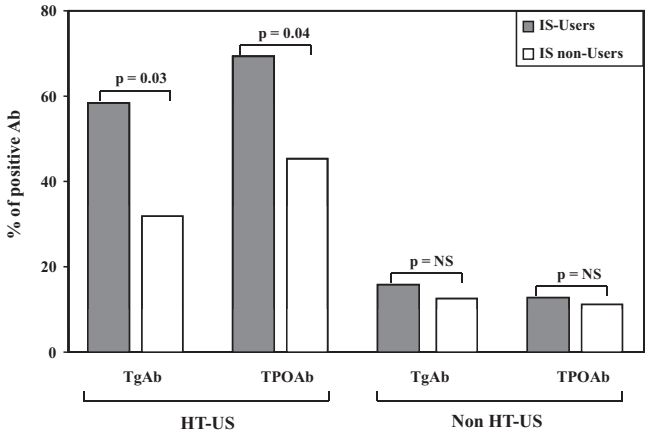

Figure 2. Frequencies of positive TgAb and TPOAb in subjects with a hypoechoic pattern at thyroid US (HT-US) and normal or slightly hypoechoic pattern (non-HT-US), according to the use of iodized salt (IS-users, *gray columns*, and IS-nonusers, *white columns*). In the 87 subjects with a HT-US pattern frequencies of both TgAb and TPOAb were significantly higher in IS-users than IS-nonusers. In the 1208 subjects with a non-HT-US pattern, the difference between IS-users and IS-nonusers was not significant for both TgAb and TPOAb (χ^2 *P* value reported).

than in IS-nonusers (median, IQR: 108 U/mL, 8–501 U/mL vs 0 U/mL, 0–53 U/mL; $P = .02$), whereas serum levels of levels of TPOAb were not significantly different between the two groups (161 U/mL, 0–588 U/mL, vs 0 U/mL, 0–434 U/mL) (Figure 3). In the 1208 subjects who had a non-HT-US pattern, no difference was observed between IS-users and IS-nonusers for both the frequency of positivity and the serum levels of TgAb and TPOAb (Figures 2 and 3).

The number of subjects with high level of TAb (ie, TgAb and or TPOAb >100 U/mL) was closely related to iodine use in HT-US subjects. Indeed, 33/65 (50.8%) IS-users and only 3/22 (13.6%) IS-nonusers had high TgAb ($\chi^2 = 9.3$, $P = .002$). For TPOAb, this difference was also significant, but to a lesser extent: 40/65 (61.5%) IS-users and 7/22 (31.8%) IS-nonusers ($\chi^2 = 5.8$, $P = .02$).

TgAb epitope pattern and use of iodized salt

TgAb epitope pattern was evaluated by inhibition experiments in 33 subjects (16 IS-users and 17 IS-nonusers) who had appropriately high TgAb levels. The highest levels of inhibition were observed for TgAb-Fab A, followed by TgAb-Fab B, C, and D (Figure 4). The levels of inhibition by TgAb-Fab region A, C, and D were similar in IS-users and IS-nonusers, as reported in Figure 3. Interestingly, inhibition by region B TgAb-Fab was significantly higher in IS-users (27.5%, 6.5–48.3%) than in IS-nonusers (3.0%, 0.0–20.5%) ($P = .047$).

Discussion

Thyroid autoimmunity is the most common organ-specific autoimmune disease. Its prevalence is linked to genetic predisposition and is also influenced by environmental factors, among which iodine plays a pivotal role (reviewed in Ref. 29). We have recently reported the prevalence of thyroid disorders in the population living in the relatively isolate, small area of Pescopagano, 15 years after the introduction of iodine prophylaxis (15). A significant increase in UIE (from a median of 55.0 μg/L to a median of 98.0 μg/L) was associated with a dramatic decrease of diffuse and nodular goiter, thyroid autonomy, and hyperthyroidism. Conversely, we observed an increased prevalence of serum TAb and hypothyroidism. The aim of the present study was to ascertain whether iodine is an important factor modulating thyroid autoimmunity and possibly to elucidate the mechanisms of this linkage. As previously discussed, environmental factors other than iodine intake could have affected the pattern of thyroid diseases in the population of Pescopagano during the 15 years elapsed between the two surveys (15). Then, we focused our analysis on the population examined in the 2010 survey, taking advantage of the higher iodine intake observed in IS-users compared to IS-nonusers. The difference in iodine intake between these two groups was slight, because iodine intake increased

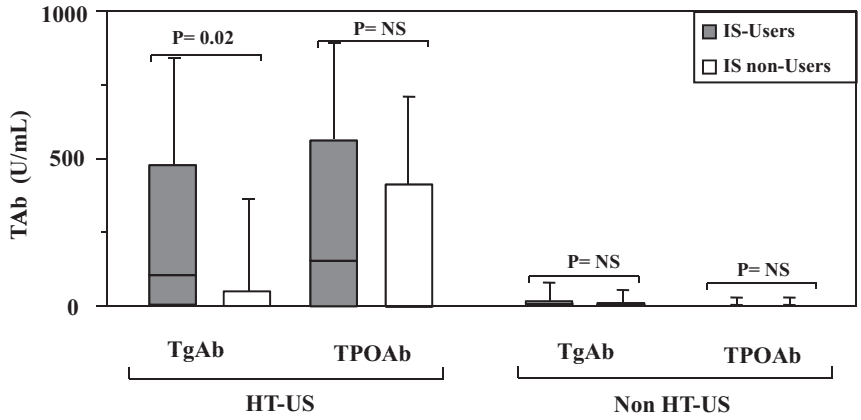

Figure 3. Box-whiskers plot of serum levels of TgAb and TPOAb in subjects with a hypoechoic pattern at thyroid US (HT-US) and normal or slightly hypoechoic pattern (non-HT-US), according to the use of iodized salt (IS-users, *gray boxes*, and IS-nonusers, *white boxes*). Results are reported as median values (*black lines*), interquartile (25th to 75th percentiles) range (*boxes*), and 10th to 90th percentiles (*whiskers*); the statistical difference between groups was evaluated using the Mann-Whitney test. In HT-US serum levels of TgAb were significantly higher in IS-users than in IS-nonusers, whereas this difference was not significant for TPOAb. In subjects who had non-HT-US pattern, no difference was observed between IS-users than in IS-nonusers for serum levels of both TgAb and TPOAb.

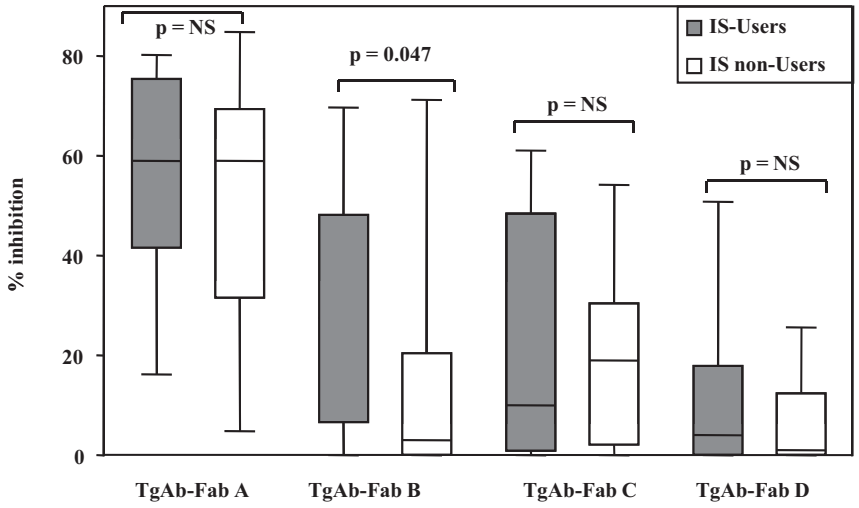

Figure 4. Box-whiskers plot of TgAb epitope pattern in 33 subjects with high (>100 U/mL) TgAb levels, 16 IS-users (*gray boxes*), and 17 IS-nonusers (*white boxes*). Results are reported as median values (*black lines*), interquartile (25th to 75th percentiles) range (*boxes*), and 10th to 90th percentiles (*whiskers*); the statistical difference between groups was calculated by Mann-Whitney test. IS-users and IS-nonusers had similar levels of inhibition by TgAb-Fab A (59%, 41.5–75.5% vs 59%, 31.5–69.5%), C (10.0%, 0.8–48.5% vs 19.0%, 2.0–30.5%), and D (4.0%, 0.0–18.0% vs 1.0%, 0.0–12.5%) (median, IQR, *P* value = NS). At variance, inhibition by region B TgAb-Fab was significantly higher in IS-users (27.5%, 6.5–48.3%) than in IS-nonusers (3.0%, 0.0–20.5%) (*P* = .047).

with respect to 1995 also in IS-nonusers, due to silent prophylaxis (30). However, even if the subjects using iodized salt had only slightly higher UIE levels, we found that positive TgAb were more common in the subgroup of subjects with higher iodine intake (IS-users) compared with those with lower iodine intake (IS-nonusers). These results are in keeping with data reported in literature, showing an increased incidence of TAb (10) after the beginning of a cautious iodization program. However, this small difference in iodine intake, together with the relatively small size of subjects examined, was probably responsible for the lack of a significant difference in the prevalence of hypothyroidism and in the frequency of HT-US pattern in IS-users vs IS-nonusers. Indeed, when we compared two populations with a higher difference in iodine intake for a longer period, we did find a significant correlation between iodine intake and hypothyroidism (15).

We have analyzed the relationship between iodine use and frequency of HT. In this survey population we confirmed that a hypoechoic thyroid US pattern is indeed closely related to HT as a consequence of thyroid lymphocytic infiltration with derangement of normal follicular structure (20–22). Thus, HT-US pattern and serum autoantibodies identify two different aspects of thyroid autoimmunity, namely, the lymphocytic infiltration of the gland and the B-cell-mediated humoral autoimmune reaction to thyroid autoantigens. The effect of iodine use was particularly evident in HT-US subjects. An association with serum TAb was indeed observed only in this subgroup of subjects, mainly for TgAb. Concomitantly, when serum levels of TAb were taken into account, in HT-US a significant increase in IS-users compared with IS-nonusers was observed only for TgAb and not for TPOAb. The number of subjects with high level of TAb (ie, TgAb and or TPOAb >100 U/mL) was also related with iodine use in HT-US subjects, mainly for TgAb. On the other hand, no significant effect of iodine was observed in subjects with a non-HT-US pattern. We conclude that iodine use is clearly associated with concomitant thyroid lymphocytic infiltration and that this correlation is more evident for TgAb than for TPOAb. This finding obtained in a survey population does not contradict the clinical observation that in full-blown HT TPOAb are more frequent than TgAb. TPOAb are indeed typical of a more advanced thyroid autoimmune involvement, are closely related with hypothyroidism (8, 31), and conceivably are more frequent in subjects seeking medical attention.

Our findings suggest that, as expected, Tg is an important target in iodine-induced autoimmune response, iodine being an essential component of Tg. Data obtained in experimental autoimmune thyroiditis confirm the pivotal role of iodine: an enhanced iodination of Tg induces a rise in TgAb levels (reviewed in Ref. 14), modifies Tg antigenicity with respect to the binding of mouse monoclonal antibodies (12), and facilitates the selective presentation of a cryptic peptide of Tg to antigen-presenting cells in mice (13).

Based on these considerations, we decided to investigate whether iodine use in humans was associated with a change in the antigenic characteristics of Tg. To this purpose we evaluated the epitope pattern on Tg recognized by TgAb, taking advantage of four human monoclonal TgAb, which recognize four different, partially overlapping regions (A, B, C, and D) on native Tg (26, 27). Sera from IS-users and IS-nonusers displayed a similar pattern of inhibition for TgAb-Fab A, C, and D, with the highest levels, as expected, for TgAb-FAb A, which identifies an epitope that is immunodominant in both autoimmune and nonautoimmune thyroid diseases (28, 32). Differently from the results obtained with the other three monoclonal antibodies, sera from IS-users showed a significantly higher inhibition of binding by TgAb-FAb B, suggesting that the epitope recognized by this monoclonal antibody is relatively hidden and is unmasked by iodine. Our recent

observation that TgAb observed transiently in subacute thyroiditis recognize B epitope at a negligible level is in keeping with B being a cryptic epitope (33).

According to these data, the rise of TgAb associated with iodine use in humans, similarly to what is observed in animals, is due to an increased immunogenicity of Tg (13; reviewed in Refs. 34–36). This may be explained by the fact that Tg is the only self-antigen that undergoes posttranslational modification as a consequence of the environmental supply of iodine, with the exposure of previously hidden epitopes. In agreement with this concept is the observation that in experimental animals iodine may play a role in central tolerance and T cells undergoing thymic selection are likely to recognize only noniodinated Tg epitopes (reviewed in Ref. 37). In accordance with data on T-cell epitope in mice (13), our data for the first time suggest that in humans the posttranscriptional iodination of Tg unmasks a cryptic B-cell epitope, which is immunogenic and induces the rise of TgAb.

The correlation between iodine intake and thyroid diseases has been described as a U-shaped curve, with optimal iodine intake overall being associated with a lower risk for abnormal thyroid function and/or thyroid autoimmunity than either inadequate or excessive intake. Our results contribute to explain the mechanism through which iodine enhances thyroid autoimmunity and why thyroid autoimmunity, including its mild and not clinically relevant form, is so common in humans. We confirm that iodine intake modulates the pattern of thyroid diseases, even for slight differences and below the dose of 150 μg daily recommended for preventing IDD (10; reviewed in Refs. 4, 38). Therefore, any level of iodine intake modifies the expression of thyroid diseases. As far as breaking of self-tolerance and induction of thyroid autoimmunity is concerned, iodine effect is correlated with the intrinsic characteristics of Tg, namely its modifications induced by posttranslational iodination.

In summary, a slight increase of iodine intake induces a rise in serum TAb, particularly TgAb; the effect of iodine is more evident in subjects with a thyroid US pattern suggestive of HT, and iodine use unmasks a cryptic Tg epitope.

We suggest that, in the presence of genetic susceptibility factors, iodine, which is essential for normal thyroid function, induces thyroid autoimmunity by unmasking a cryptic epitope on Tg. The clinical manifestations that result from this autoimmune reaction range from a mild phenotype in which only low levels of serum TAb, and particularly TgAb, are detectable to a more advanced one, characterized by high levels of TgAb and TPOAb, thyroid lymphocytic infiltration, and eventually hypothyroidism.

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