

# High Prevalence of Thyroid Dysfunction and Autoimmune Thyroiditis in Adolescents After Elimination of Iodine Deficiency in Eastern Black Sea Region of Turkey

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In the present study we evaluated the effects of iodine intake on the prevalence of thyroid dysfunction, autoimmunity and goiter in two regions with different iodine status after two years of iodination in Turkey.

A total of 1733 adolescent subjects were enrolled into the study (993 from iodine sufficient area- Eastern Black Sea Region (group 1), 740 from iodine deficient area- Middle Anatolia (group 2). We measured free thyroxine (FT4), thyrotropin (TSH), antithyroid peroxidase antibodies (Anti-TPO), antithyroglobulin antibodies (Anti-Tg), and urinary iodine (UI), and examined the thyroid gland by ultrasound. Median urinary iodine excretion was found to be significantly different in group 1 and group 2 (139 µg/l vs. 61 µg/l,  $p<0.001$ ). Hyperthyroidism was more frequent in group 1 (3.6% vs 0.7%;  $p<0.001$ ), but hypothyroidism rate was similar between groups (1.8% vs 1.4 %;  $p>0.05$ ). The percentage of anti-Tg positive subjects was found to be 17.6% in group 1 and 6.4% in group 2, and that of anti-TPO positive subjects was 4.3% in group 1 and 1.5% in group 2. The prevalence of antithyroid antibody (anti-Tg and/or anti-TPO) positivity was significantly higher in group 1 than in group 2 (18.52% vs 6.62%;  $p<0.001$ ). Thyroid volumes of the hyperthyroid subjects in both groups were significantly higher than hypo and euthyroid subjects. In conclusion, iodine supplementation in Turkey has resulted in the elimination of iodine deficiency in Eastern Black Sea Region, and this has been accompanied by an increase in the prevalence of autoimmune thyroiditis and thyroid dysfunction.

**Keywords:** iodine supplementation, thyroid autoimmunity, thyroid dysfunction

## Introduction

Iodine is an essential trace element, necessary for the synthesis of thyroid hormones. Iodine metabolism and thyroid function are closely linked. The recommendation of the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), is that adequate iodine intake be between 100 and 199 µg/L based on median urinary iodine excretion in school-aged children

(1). Because iodine deficiency is one of the most important major public health problem all over the world, iodine prophylaxis is being suggested to solve this problem. The control of the efficiency and the results of iodination programs can be done clinically, biochemically and by monitoring the side effects (2). In spite of the fact that clinical improvement is the most important end-point, side-effects of iodine excess is not generally taken into consideration. Although majority of individuals tolerate a wide range of dietary iodine levels, a subset of individuals develop thyroid dysfunction and autoimmunity upon exposure to elevated or even normal levels of iodine. A deficient intake of iodine may result in goiter and hypothyroidism. However, elimination of iodine deficiency may result in hyperthyroidism. After the increment in iodine intake, an increased

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incidence of hyperthyroidism was observed in many previously iodine deficient areas (3, 4,5).

Definitive proof of the existence and extent of iodine induced hyperthyroidism has been provided by studies in Tasmania (6,7). Moreover, patients with underlying thyroid disease, such as Hashimoto's thyroiditis are particularly susceptible to developing iodine-induced hypothyroidism over the ensuing several weeks after the exposure (8). On the other hand, both iodine deficiency as well as iodine excess may lead to thyroid autoimmunity, albeit in genetically different individuals (9). It has been argued in the literature that introduction of iodine in a previously iodine deficient population may precipitate the emergence of thyroid autoimmunity (10).

According to some studies, iodine supplementation in iodine deficient areas increases the prevalence of thyroid autoantibody positivity and lymphocytic infiltration of thyroid gland (10-13). It has been reported that in previously endemic areas of Greece, the predominant form of nontoxic goiter in schoolchildren now seems to be autoimmune thyroiditis (14). On the basis of the changing incidences of autoimmune thyroid disease and of the iodine-induced effects on the thyroid in animals and man, it has been suggested that iodine could be hold responsible for triggering or enhancing the onset and development of autoimmune thyroid disease. Iodine prophylaxis is essential in iodine-deficient areas, but these side-effects of iodine excess has to be taken account as well, while evaluating the efficiency of the iodination. Before the mandatory iodination, Turkey was an iodine deficient area in general (15). New data show that iodine status of the certain regions have changed. Some areas have become iodine sufficient whereas iodine deficiency improved but not reached to desired levels in some others. So not only the goiter prevalence, but also the prevalence of thyroid autoimmunity and thyroid dysfunction are expected to be changed. In the present study, we evaluated the effects of iodine intake on the prevalence of thyroid dysfunction, autoimmunity and goiter in two regions with different iodine status after two years of iodination in Turkey.

## Subjects and Methods

The study was done in two regions with different iodine status after two years of iodination in

Turkey. Totally 1733 adolescents, between 14-18 years of age, were enrolled into the study. Of these, 993 were in an iodine sufficient area which is located in Eastern Black Sea Region and consisted of group 1, while the rest 740 were from an iodine deficient area which is located in Middle Anatolia and consisted of group 2. These two regions were known to be iodine deficient areas before iodination (15). The mean ages and the sex distribution were matched between group 1 and group 2 (mean ages were  $15.43 \pm 1.03$  and  $15.43 \pm 0.98$  years, respectively;  $p > 0.05$ , and male/female ratios were 521/472 and 360/380, respectively;  $p > 0.05$ ). Spot urine sample were collected for measurement of urinary iodine excretion. Blood samples for thyroid functions and thyroid autoantibodies were collected from all the subjects as well.

## Laboratory methods

The thyroid was examined and its volume measured by using a real time B mode, high resolution, General Electric sonography (Hino-shi, Tokyo, Japan) with a 7.5 MHz probe. Thyroid volumes were calculated using the formula (height (a) x length (b) x thickness (c) x  $\pi/6$ ). The volumes of both thyroid lobes were calculated separately and the sum of the volumes of both lobes was accepted as thyroid volume (16, 17). For the determination of goiter, World Health Organization and International Council for Control of Iodine Deficiency Disorders criteria were used. Thyroid volume over 13.9 ml in boys and 14.6 ml in girls for 14-year old adolescents and thyroid volumes over 16.0 ml in boys and 16.1 ml in girls for 15- to 18- year old adolescents were accepted as goiter (18, 19).

Blood samples were centrifuged immediately after collection. Both urine and serum samples were stored at  $-80^{\circ}\text{C}$  until assay.

Free thyroxine (FT4) analysis was based on competitive, direct chemiluminassay by using an ACS:180 (Bayer Corporation, New York, NY, USA) kit and results were calculated as pmol/l. Thyrotropin (TSH) measurements were based on direct immunoassay using the ACS:180 kit. TSH results are expressed as mIU/l. Anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibodies were determined as the thyroid

autoantibodies. For anti-Tg analysis, immunoradiometric assay with immunoradiometric coated tube (BC 1006-Biocode, Liege, Belgium) kit and for anti-TPO analysis, radioimmunoassay (RIA) with One Step RIA coated tube (BC 1008-Biocode) kit were used. Anti-Tg and anti-TPO results are expressed as IU/ml. Anti-Tg levels over 10 IU/ml and anti-TPO levels over 15 IU/ml were accepted as autoantibody positivity (20). Urinary iodine excretion was determined using an enzymatic method, the Sandell-Kalthoff method, with Fischer reagents and using spectrophotometry (21). Results are expressed as  $\mu\text{g/l}$ .

### Statistical Analysis

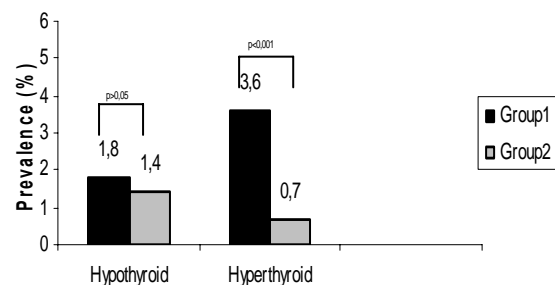
Urinary iodine excretion, thyroid function tests and the thyroid autoantibody levels were compared with the Mann-Whitney U test. The Chi square test, as appropriate, was also used to compare the goiter prevalence, autoantibody positivity prevalence in group 1 and 2. Data are given as mean  $\pm$  S.D. or median. A P value  $<0.05$  was accepted as significant.

### Results

It has been demonstrated in previous studies that before the mandatory iodination, Eastern Black Sea Region and Middle Anatolia were iodine deficient areas (15, 22). Table 1 shows the comparison of the thyroidal results between groups. In our study, median urinary iodine excretion was found to be significantly different in these regions ( $139 \mu\text{g/l}$  vs.  $61 \mu\text{g/l}$ ,  $p<0.001$ ). According to WHO classification, group 1 was representative for iodine sufficiency and group 2 was a mildly iodine deficient area. As would be expected, thyroid volumes were found to be significantly lower in group 1 than in group 2 ( $14.0 \pm 5.0$  vs.  $17.6 \pm 5.6$  ml  $p<0.001$ ). Similar results were obtained when the mean thyroid volumes of the different sexes were compared between groups.

In group 1, normal serum TSH levels were determined in 939/993 (94.6%) subjects, so they were euthyroid. On the other hand, 18/993 (1.8%) subjects in group 1 had serum TSH concentration over the normal range ( $>5$  mIU/l), but their serum FT4 levels were found to be normal. So they had subclinical hypothyroidism. Subnormal ( $<0.4$  mIU/l) or undetectable ( $<0.01$  mIU/l) serum TSH

concentrations were found in 36/993 (3.6%) subjects in group 1. Of these 36 subjects, only two had high serum FT4, so they had overt hyperthyroidism. The rest 34 subjects had subclinical hyperthyroidism. In group 2, 725/740 (98%) subjects had normal serum TSH and FT4 levels. However, 10/740 (1.4%) subjects in this group had supranormal TSH concentration ( $>5$  mIU/l) and the rest 5/740 (0.7%) subjects had subnormal ( $<0.4$  mIU/l) or undetectable ( $<0.01$  mIU/l) serum TSH concentration. All the subjects with thyroid dysfunction in group 2 had normal FT4 levels, so no subjects with overt hypo- or hyperthyroidism was found in group 2. Hyperthyroidism was more frequent in group 1 (3.6% vs 0.7%;  $p<0.001$ ), but hypothyroidism rate was similar between group 1 and group 2 (1.8% vs 1.4%, respectively;  $p>0.05$ ), as shown in figure 1. Thyroid volumes of the hyperthyroid subjects in group 1 and group 2 ( $19,13 \pm 7,94$  ml in group 1 and  $21,85 \pm 4,71$  ml in group 2) were significantly higher than hypo ( $13,58 \pm 4,53$  ml in group 1 and  $17,64 \pm 7,14$  ml in group 2) and euthyroid ( $13,81 \pm 4,84$  ml in group 1 and  $17,61 \pm 5,60$  ml in group 2) subjects, and the differences were statistically significant ( $p<0.001$  for all comparisons).



**Figure 1.** Prevalence of hyperthyroidism and hypothyroidism in subjects of Group 1 and Group 2

Thyroid autoantibody levels were significantly different between group 1 and group 2. The mean anti-Tg level was found to be higher in group 1 ( $63.02 \pm 389.43$  vs  $28.44 \pm 145.60$  IU/ml;  $p<0.001$ ) and mean anti-TPO level was higher in group 2 ( $20.28 \pm 203.47$  vs  $33.51 \pm 249.61$  IU/ml;  $p<0.001$ ). The prevalence of antithyroid antibody (anti-Tg and/or anti-TPO) positivity was significantly higher in group 1 than in group 2 (18.52% vs 6.62%;  $p<0.001$ ). The percentage of anti-Tg positive subjects was found to be 17.6% in group 1 and 6.4% in group 2, and that of anti-TPO

**Table 1.** Comparison of the thyroïdal outcomes between group 1 and group 2

	Group 1	Group 2	p
Urinary iodine excretion ( $\mu\text{g/l}$ )	139	61	$<0,001^a$
FT4 (pmol/l)	$17.12 \pm 2.98$	$16.80 \pm 2.78$	NS <sup>a</sup>
TSH (mIU/l)	$2.19 \pm 1.31$	$2.20 \pm 1.79$	NS <sup>a</sup>
Thyroid volume (ml)	$14.0 \pm 5.0$	$17.6 \pm 5.6$	$<0,001^a$
Prevalence of goiter (%)	28.25	61.95	$<0,001^b$
Anti-Tg (IU/ml)	$63.02 \pm 389.43$	$28.44 \pm 145.60$	$<0,001^a$
Anti-TPO (IU/ml)	$20.28 \pm 203.47$	$33.51 \pm 249.61$	$<0,001^a$
Percentage of thyroid autoantibody-positive subjects (%)	18.52	6.62	$<0,001^b$

Urinary iodine excretion is given as median and free T4, TSH, thyroid volume, anti-Tg and anti-TPO were given as median  $\pm$  standart deviation  
 NS: Not significant,  $\alpha$ : Mann-Whitney U test,  $\beta$ : Chi-square test

**Table 2.** Comparison of the thyroïdal results in euthyroid, hyperthyroid and hypothyroid subjects in both groups.

	Euthyroid subjects (n=1595)	Hyperthyroid subjects (n=41)	Hypothyroid subjects (n=28)	p*
Median urinary iodine excretion ( $\mu\text{g/l}$ )	114.5	166.5	159.0	$<0.001^a$
Mean thyroid volume (ml)	$13.8 \pm 4.8$	$19.1 \pm 7.9$	$13.5 \pm 4.5$	$<0.001^b$
Mean anti-Tg (IU/ml)	$50.4 \pm 338.9$	$136.4 \pm 376.9$	$81.2 \pm 285.8$	$<0.05^c$
Mean anti-TPO (IU/ml)	$21.0 \pm 274.0$	$182.7 \pm 837.2$	$65.2 \pm 219.0$	$<0.05^a$
Percentage of thyroid autoantibody positivity (%)	12.4	31.7	10.7	$<0.001^b$

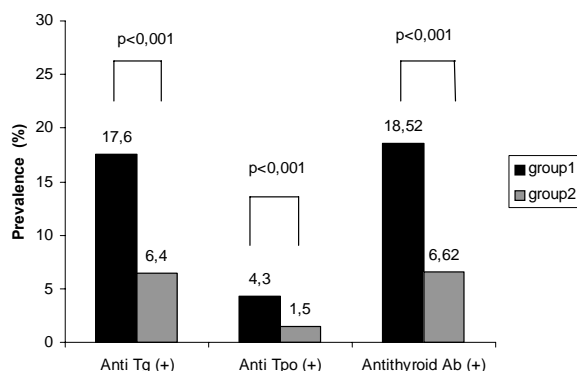
\*Chi-square test

a-Euthyroid subjects are significantly different than hiper- and hypothyroid subjects

b-Hypertiroid subjects are significantly different than hypo- and euthyroid subjects

c-Hyperthyroid subjects are significantly different than euthyroid subjects

positive subjects was 4.3% in group1 and 1.5% in group2. Figure 2 shows the comparison of the thyroid autoantibody positivity between groups.

**Figure 2.** Prevalence of thyroid antibody positivity in Group 1 and Group 2

As expected, thyroid autoantibody positivity was higher among females when compared with males

in both groups, but the difference was not significant (in group 1, 13.6% for males, 23.9% for females; in group 2, 4.16% for males, 8.9% for females). Comparing the percentage of autoantibody-positive males and females, there was significant difference between the groups ( $p < 0.001$  and  $p < 0.001$ , respectively).

Comparison of urinary iodine excretions, thyroid volumes, mean anti-Tg and anti-TPO levels, as well as percentage of thyroid autoantibody positive subjects of euthyroid, hyperthyroid (overt and subclinical) and subclinical hypothyroid subjects including all subjects in both groups is shown in table 2.

When all subjects were taken into consideration, thyroid volumes of the hyperthyroid subjects were significantly higher than hypo and euthyroid subjects ( $p < 0.001$  and  $p < 0.001$  respectively).

Urinary iodine excretions were also found to be significantly higher in both hyper and hypothyroid subjects when compared to euthyroid subjects ( $p<0.001$  and  $p<0.001$ , respectively). Comparing with normal subjects, mean anti-Tg and anti-TPO levels were found to be significantly higher in hyperthyroid subjects ( $p<0.05$  and  $p<0.05$ , respectively), but there were no significant difference between hyperthyroid and hypothyroid subjects. Hypothyroid subjects had significantly higher mean anti-TPO level comparing with euthyroid subjects ( $p<0.05$ ), but mean anti-Tg level was not different between hypo and euthyroid subjects. Percentage of thyroid autoantibody positive subjects was also higher in hyperthyroid subjects than hypo and euthyroid subjects ( $p<0.001$  and  $p<0.001$ , respectively).

## Discussion

Thyroid gland has the capacity and holds the machinery to maintain the synthesis and secretions of thyroid hormones even when the availability of iodine becomes scarce, or when it is available in excessive amounts (8).

It is still controversial whether completely normal subjects may develop perturbed thyroid function or thyroid autoimmunity when these subjects are exposed to large doses of iodide. On the other hand, the well known side effects of iodine include iodine induced hyperthyroidism and hypothyroidism (2). In addition, introduction of iodine in a previously iodine deficient population may precipitate the emergence of thyroid autoimmunity (10, 23, 24).

To investigate the effect of different iodine intakes on the prevalence of goiter, thyroid dysfunction, and thyroid autoimmunity, we performed a comparative cross-sectional survey in two areas with median urinary excretion of 139 ug/L and 61 ug/L, in Turkey, after two years of mandatory iodination. The two commonest methods of monitoring of iodine supplementation program are urinary iodine estimation and goiter rate. The urinary iodine excretion was different between the two groups. Urinary iodine excretion results suggested that the iodination programme has been effective in group 1.

The lower prevalence of goiter in group 1 may have reflected a genuine reduction in thyroid volume with continuing exposure to iodine. Although goiter prevalences in both sexes and mean thyroid volumes were found to be significantly lower in the iodine-sufficient area, it was noticeable that goiter was still endemic in both regions. It was because the time of the iodine prophylaxis had not been enough for the reduction of goiter prevalence yet. It has also been demonstrated that decrease in goiter takes time to be achieved after the increment in iodine intake (25, 26). Using criteria recommended by WHO (27) for defining the severity and prevalence of IDD as a public health problem, Middle Anatolia may be labelled as having a moderate IDD problem based on clinical measurement of thyroid size and mild IDD based on biochemical indicators.

A significantly higher level of anti-Tg antibody was found in the subjects with sufficient iodine intake. The increase in iodine intake that occurs when iodine supplementation may have induced the greater prevalence of anti-Tg positivity in group 1 in comparison with group 2. It has been argued in the literature that introduction of iodine in a previously iodine deficient population may precipitate the emergence of thyroid autoimmunity (10, 23). This finding was also in accordance with the results of a study from Japan with recognized excessive iodine intake (28). The immune modulatory effects of iodine are well documented (29, 30). There are experimental animal and human data to suggest that iodinated thyroglobulin is much more immunogenic than poorly iodinated one (30-32). Antithyroid autoantibodies may be the result of the high iodine intake (33-35). The coexistence of anti-Tg and anti-TPO could be a clinical expression of more intense autoimmune process, as suggested previously (36, 37). In spite of the fact that the percentage of autoantibody-positive subjects was higher in females than males, the difference was not significant in any region. Both mean anti-Tg and anti-TPO levels were found to be significantly higher in female subjects than in male subjects of group 1. It is well known that autoimmune thyroid diseases are more frequent in females (38).

The prevalence of hyperthyroidism (overt or subclinical) was found to be more frequent in the

iodine-sufficient area than in the mildly iodine-deficient area (3.6% vs 0.7%, respectively), but the prevalence of hypothyroidism did not differ between regions (1.8% vs 1.4%, respectively). Iodine supplementation to an iodine deficient population may be accompanied by an increase in the incidence of hyperthyroidism (3- 5). This may explain the greater percentage of hyperthyroidism in group 1 compared with group 2. The increase is associated with a rapid correction due to the recent excessive increment in iodine intake (2 years) and the duration as well as the severity of the previous iodine deficiency (39, 40). Hyperthyroidism in both groups may be related to thyroid autoimmunity and thyroid autonomy.

It is established that thyroid autonomy due to long term iodine deficiency may lead to hyperfunction (41, 42). The significantly higher prevalence of thyroid autoantibody in subjects with hyperthyroidism in both groups suggests that hyperthyroidism may be partly related to thyroid autoimmunity. This is in accordance with the results of a study from China (43). In the previous studies, the frequency of goiter in subjects with subclinical hyperthyroidism was significantly higher than in subjects with normal TSH (44). Our findings are also in accordance with the findings that thyroid enlargement was found to be more prevalent in subjects with suppressed TSH than in subjects with normal TSH. The greater prevalence of goiter in subjects with subclinical hyperthyroidism may have favoured the occurrence of thyroid autoimmunity, as there is evidence to suggest that the mechanisms involved in goiter formation do predispose to thyroid autoimmunity (45). Iodine induced thyroid autoimmunity is another side effect of iodine prophylaxis. In our study, although the percentage of thyroid autoantibody positive subjects did not differ between hypothyroid and euthyroid subjects, it was significantly higher in hyperthyroid subjects. Beside this, mean anti-Tg and anti-TPO levels were higher in hyperthyroid subjects when compared with euthyroid ones.

In the Sardinian autoimmunity study, anti-thyroid autoantibodies was found to be associated with an increased prevalence of subclinical hypothyroidism (46). Resembling to this study, we found significantly higher anti-TPO level in hypothyroid subjects when compared with euthyroid subjects. It

seems that persons with positive anti-thyroid autoantibodies are especially prone to the development of thyroid dysfunction after iodine excess.

In conclusion, after two years of iodination, iodine deficiency successfully eliminated in Eastern Black Sea Region of Turkey, but not in the Middle Anatolia. These results show that iodine supplementation in iodine deficient areas triggers thyroid autoimmunity and causes thyroid dysfunction even in younger individuals. Hyperthyroidism is more frequent and anti-TPO positivity might be a risk factor for the development of hypothyroidism upon exposure to iodine.

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