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PREVALENCE OF HYPERTHYROIDISM IN ISFAHAN-IRAN, IN THE YEAR 2006, FIFTEEN YEARS AFTER UNIVERSAL SALT IODIZATION: A COMMUNITY BASED STUDY

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Abstract

The objective of this study was to investigate the prevalence of hyperthyroidism in Isfahan, a centrally located city in Iran, fifteen years after universal salt iodization.

In a cross-sectional study, 2523 Isfahani adult people (aged >20 years, 1275 men and 1248 women) were selected by multistage cluster sampling method. TSH was measured in all (n=2523) and urinary iodine concentration (UIC) in one fourth of participants. Those with low TSH <0.3 mIU/L were recalled and re-tested (n=115). Low TSH with normal FT4I and T3 at the second measurement was considered as subclinical and low TSH with high FT4I or T3 as overt hyperthyroidism. TPOAb, TgAb and UIC were measured in hyperthyroid patients and controls.

The prevalence of hyperthyroidism was 1.8 % (n=46): overt-0.8% (n=21) and subclinical hyperthyroidism 1.0% (n=25). Hyperthyroidism was observed in 2.6% of women (n=32) and 1.1% of men (n=14) (OR= 2.4, CI 95%: 1.3-4.5, P=0.006). Iodine deficiency and excess were observed in 21.4% and 18.7% of all population, being 38% and 33% in hyperthyroid patients, respectively (P>0.05). Thyroid function had no statistically significant correlation with iodine intake status. Nobody had UIC more than 100 µg/dl. The prevalence of positive TPOAb and/or TgAb was 54.5% and 29.2% in hyperthyroid and euthyroid people, respectively (OR= 2.9, CI 95%: 1.2-7, P=0.01).

*Conclusions:*The rate of hyperthyroidism in our region was similar to iodine sufficient areas. Its development is not a direct effect of iodine intake. Antithyroid autoimmunity may have a role.

Key words: Hyperthyroidism, Iran, iodine, autoimmunity.

INTRODUCTION

Subclinical and overt thyroid disorders are common in population, even in those which considered iodine replete (1-5).The prevalence of thyroid disorders

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varies with age, gender and across ethnic and geographic regions (6-9). Genetic factors, autoimmunity and also some environmental factors such as iodine intake have some influence in thyroid abnormalities in a population (10-12).

Hyperthyroidism is emerging as potential contributor to morbidity from osteoporosis, cardiovascular effects such as atrial fibrillation and neurosychatric symptoms (13, 14).

In the third National Health and Nutrition Examination Survey (NHANES III) (5), the large population – wide survey in the United States, hyperthyroidism was found in 1.3% (0.5% overt and 0.7% subclinical) of the total population. In Iran, Haydarian et al, in a study which was done in the East part of Tehran (not all over the city), during 1999-2000, 10 years after implementation of universal salt iodization, have reported a prevalence of 0.42% of hyperthyroidism (all subclinical forms)(15). Forty mg of potassium iodide has been added per kg of salt, for iodine supplementation in Iran (16).

The prevalence and pattern of thyroid disorders depends on ethnic and geographic factors, including iodine intake status (17, 18). In order to determine an appropriate strategy for screening of thyroid disorders in our community, fifteen years after universal salt iodization, this study was conducted in 2006 in Isfahan, which has been considered as an iodine replete area in the central part of Iran (19). This is the first epidemiologic study which was done in all parts of a big city (two million population) in Iran.

A national survey of goiter in 1989 (before iodized supplementation) showed that the prevalence of goiter in schoolchildren of most provinces with rates between 30% and 70%. It was more than 70% in Isfahan province and 92% in girls and 85% in boys of its capital, Isfahan city (20). At the same time, median urinary iodine excretion was under 100 μg/L in all localities and less than 20 μg/L in many localities examined (21). There were no published data about high neonatal TSH (>5 mIU/L) before salt iodization. However, there were some studies that showed the occurrence of physical, psychomotor disturbances and intellectual impairment in apparently normal schoolchildren from iodine deficiency areas in Iran (22, 23).

SUBJECTS AND METHODS

In a cross-sectional study, 2600 Isfahani adults were selected by the multistage cluster sampling method. At first stage, we randomly selected 40 blocks on the city map. Then, we asked the post office to give us the addresses of all the homes in each block. We randomly selected 960 addresses from the post office list (24 homes in each block). In this way, 2600 adult people were invited; 2523 (97% of invited people) accepted our invitation and came for examination and testing from January till April 2006. They were aged ≥20 years, mean age 39 (±12.4) years, range: 20-86 years, 1275 men (50.5%) and 1248 women (49.5%). People were informed and invited to enroll the study door to door by trained personnel. Consents were

obtained from participants before recruitment to the study. People were asked to come to Isfahan Endocrine and Metabolism Research Center (IEMRC), according to a pre-planned appointment. Seven trained general practitioners asked them questions about demographic data, past history of thyroid disorders, their past or current medications, including iodine supplementations (vitamins), iodine overload (amiodarone) or other drugs that could interfere with thyroid function (glucocorticoids) and observed their past medical documents and files and filled out a detailed questionnaire, designed by us, for each person. Our study was in accordance with the ethical standards of the IEMRC committee on human experimentation and with the Helsinki Declaration. It was approved by the Regional Committee for Ethics of IEMRC and Isfahan University of Medical Sciences.

Those who had any history of thyroid disorders or abnormality on physical examination or laboratory finding were re-called to be visited by an endocrinologist. On this occasion, the TSH result of all participants was mailed to them. The interval between the first examination and recalled invitation was about 2-3 weeks. We reported goiter according to the two-grade classification system proposed by WHO/ International Council for the Control of Iodine Deficiency Disorders (ICCIDD) in 1994 (24).

Serum TSH, T4, T3 and Thyroid autoantibody assays

Blood samples were obtained from all participants (n=2523). In one fourth of randomly selected subjects, urine samples were collected and iodine concentration was measured. Both collected serum and urine samples were frozen at -20°C, in the IEMRC laboratory. People who had low TSH concentration <0.3 mIU/L (n=115) and those who were known as cases of hyperthyroidism were recalled and visited by an endocrinologist (AA). In those who were not on treatment, second blood samples were collected to measure TSH, T4, T3 and T3RU. Free T4 Index (FT4I) was calculated as T4*T3RU. TSH was measured by IRMA (Kavoshyar kits, Tehran, Iran), with intra-assay and inter-assay CV of 1.5% and 1.9%, respectively, and normal range 0.3-4 mIU/L.

Serum T4 was assayed by radio-immunoassay (RIA) (Kavoshyar kits, Tehran, Iran), with intra- and inter-assay CV of 4.7% and 4.9%, respectively and normal range for T4 of 4.5-12 μg/dl. Normal range for T3 concentration was 70-190 ng/dl. T3RU was assayed by RIA (Kavoshyar kits, Tehran, Iran), with intra- and inter-assay CV of 3.6% and 4.4%, respectively. Normal range for T3RU concentration was 25%-35%. Normal range for FT4I according to our laboratory was 1.35-4.8.

AntiTg and AntiTPO were measured by Rapid ELISA (Genesis Diagnostic Co.). Intra-assay and inter-assay CV for AntiTg was <12% and for AntiTPO was 7% and 5%, respectively. AntiTg and AntiTPO concentrations more than 100 IU/ml and 75 IU/ml, respectively, were considered positive.

Low TSH (<0.3 mIU/L) level with normal FT4I and T3 at second measurement was considered subclinical hyperthyroidism and low TSH with high FT4I or T3 as overt hyperthyroidism (25). The same criteria were considered to diagnose hyperthyroidism according to previous documents of known cases of hyperthyroidism (14 out of 25 patients in subclinical and 15 out of 21 patients in overt

hyperthyroidism subgroup). Five patients with overt hyperthyroidism were on methimazole and 10 patients were on remission after 1-2 years of thionamide therapy. Therefore, the thyroid function tests of 6 out of 21 patients in overt hyperthyroidism subgroup were reported. In subclinical hyperthyroidism subgroup (n=25), one patient was on treatment, as he had coronary artery disease. Nine people who had low TSH did not come to us on recall. We classified them in subclinical group. However, thyroid function tests were reported in 15 patients. Autoantibodies were measured in 22 patients with hyperthyroidism: 12 patients in subclinical and 10 patients with overt hyperthyroidism subgroup. One patient in overt hyperthyroidism and 5 patients in subclinical hyperthyroidism subgroup had thyroid nodules at physical examination. Graves was diagnosed according to both laboratory data and clinical manifestation (ophthalmopathy, diffuse goiter, etc.). Controls were selected randomly from euthyroid participants to measure autoantibodies (n=295); in 142 out of these, T4, T3, T3RU and TSH concentrations were measured.

Urinary iodine concentration was measured by the digestion method based on a modification of Sandell-Kolthoff reaction; intra-assay and inter-assay CV was 1.25% and 2.2%, respectively (25). Urinary iodine concentrations (UIC) less than 10 µg/dl were considered as iodine deficiency and UIC>30 µg/dl as iodine excess and between as iodine sufficiency (26).

The data were analyzed with SPSS ver.13 software and Epi 6.04. Variables with normal distribution are expressed as mean (±SD). Those variables, which were not normally distributed were expressed as median (range). The prevalence of overt and subclinical hyperthyroidism in different age (<= 30, 31-40, 41-50 and>50 years old), sex groups and according to UIC was compared with ANOVA and Chi-square test. Correlation between quantitative variables was calculated by Pearson correlation coefficient. P-values less than 0.05 were considered statistically significant.

RESULTS

Of the 2523 studied population, mean age was 39 (±12.4), range: 20-86 years, 1275 were men, mean age 41 (±12.7), range: 20-80 years, and 1249 were women, mean age 37 (±12.4),range: 20-86 years .The overall prevalence of hyperthyroidism (both overt and subclinical) was 1.8% (46 persons, including 5 patients who were known cases of hyperthyroidism and were on thionamide treatment) and the prevalence of subclinical and overt hyperthyroidism was 1% (n=25) and 0.8% (n=21), respectively. Overall, 2.6% of women (n=32) and 1.1% of men (n=14) were hyperthyroid, (OR= 2.4, CI 95%: 1.3-4.5, P=0.006).

Six out of 46 hyperthyroid people had toxic multinodular goiter. Forty out of 46 people had Graves' disease. None of hyperthyroid patients had toxic adenoma, iodine-induced hyperthyroidism, trophoblastic disease, germ cell tumors and TSH-mediated hyperthyroidism. Seventeen out of 46 hyperthyroid persons had no goiter (37%), 14 people had grade 1 (30.4%) and 15 persons (32.6%) grade 2 goiter

Table 1. Prevalence of subclinical and overt hyperthyroidism in adult Isfahani population: according to the age groups and gender in 2006

	Subclinical (np/n) (%)	Overt (np/n) (%)	All (np/n) (%)
Men			
<=30	1/308(0.3%)	0/308 (0.0%)	1/308(0.3%)
31-40	2/323(0.6%)	3/323 (0.9%)	5/323(1.5%)
41-50	4/394(1.0%)	2/394 (0.5%)	6/394(1.5%)
>50	2/250(0.8%)	0/250 (0.0%)	2/250(0.8%)
Total (men)	9/1275 (0.7%)	5/1275 (0.4%)	14/1275 (1.1%)
Women			
<=30	5/448(1.1%)	6/448 (1.3%)	11/448(2.4%)
31-40	3/319(0.9 %)	4/319 (1.3%)	7/319(2.2 %)
41-50	3/273(1.1%)	5/273 (1.8%)	8/273(2.9%)
>50	5/208(2.4%)	1/208 (0.5%)	6/208(2.9%)
Total (women)	16/1249 (1.3%)	16/1249 (1.3%)	32/1248 (2.6%)
Total			
<=30	6/756(0.8%)	6/756(0.8%)	12/756(1.6%)
31-40	5/642(0.8%)	7/642(1.1%)	12/642(1.9%)
41-50	7/667(1.1%)	7/667(1.1%)	14/667(2.2%)
>50	7/458(1.5%)	1/458(0.2%)	8/458(1.7%)
Total	25/2523 (1%)	21/2523 (0.8%)	46/2523 (1.8%)

np=number of patients with hyperthyroidism
n= number of all studied population

according to WHO criteria (24).

Prevalence of goiter in the studied general population (2523) was 19% (n=478), of whom 12.4% (n=312) had grade 1 goiter and 6.6% (n=166) had grade 2. The prevalence of the two subgroups of hyperthyroidism according to age and sex groups is shown in Table 1.

From women subjects, 224 out of 1248 were menopausal and 3/224 menopausal women were hyperthyroid (1.3%). Prevalence of hyperthyroidism was not higher in menopausal women. Age distribution of all studied population (n=2523) and hyperthyroid group (n=46) is shown in Fig. 1. None of people older than 60 years had hyperthyroidism, although 117 (4.6%) of the general population were older than 60 years. Using EPI 6.04, there was no difference between age groups in the prevalence of hyperthyroidism (P=0.5). Median (range) of TSH, T4, and mean (SD) of T3, T3RU, FTI in hyperthyroid patients excluding known cases who were on treatment or in remission were reported in Table 2.

Urinary iodine concentration (UIC) was measured in 710 participants. Median of UIC was 18 µg/dl (range: 1-80 µg/dl) for all studied participants; it was 22µg/dl

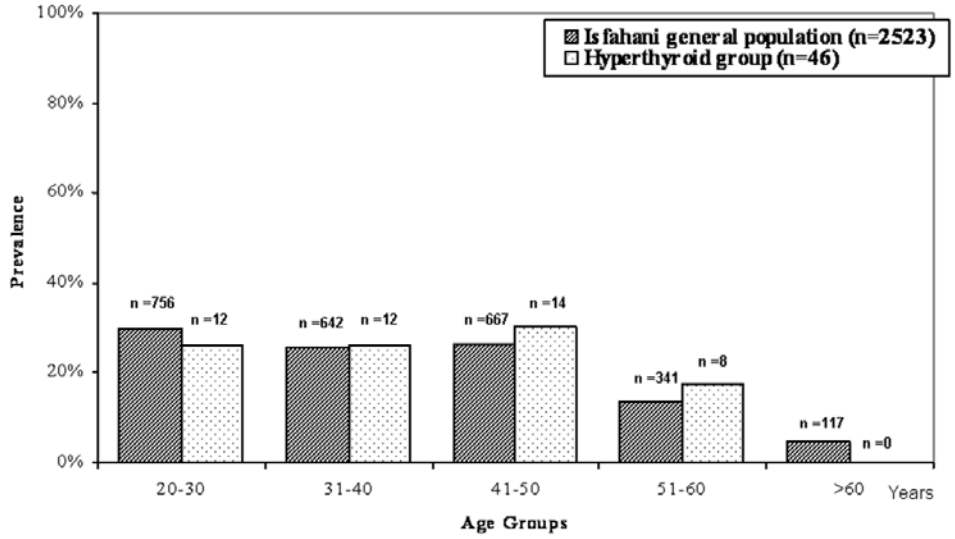

Figure 1. Age distribution of studied Isfahani general population and hyperthyroid group in 2006.

and 22.7 µg/dl for subclinical and overt hyperthyroidism, respectively. Mean of UIC in hyperthyroid people whose iodine intake examined was 24.5 (±14.1) µg/dl and it was 20.4 (±12.9) µg/dl in non-hyperthyroid persons. Iodine deficiency, sufficiency and excess were observed in 152 (21.4%), 425 (59.9%) and 133 (18.7%) of the studied population, respectively (P<0.01). In hyperthyroid patients, 7 (38%), 6 (28.6%) and 8(33%) were iodine deficient, sufficient and excess, respectively (P>0.05). There were not significant differences between UIC and the prevalence of clinical and subclinical hyperthyroidism (P>0.05). The status of thyroid autoantibodies in hyperthyroid and healthy subjects was presented in Tables 2 and 3. TPOAb and TgAb positivity was more prevalent in hyperthyroidism.

DISCUSSION

This study indicated the prevalence of overt and subclinical forms of hyperthyroidism among the population of Isfahan city aged 20 years and older, fifteen years after implementation of salt iodization. There was not significant correlation between hyperthyroidism and increasing age. It was not higher in people older than 50 or in menopausal women (Table 1). The etiology of hyperthyroidism in most of our studied population was Graves' disease. Therefore, it seems that non-autoimmune hyperthyroidism is less prevalent than the etiology of hyperthyroidism in our studied population. It can explain why the prevalence of hyperthyroidism is not higher in people aged over 60 years in comparison with younger people. Another

Table 2. Mean (SD) or median (range) of second measurement of T4, TSH, T3, T3RU, FT4I and TPOAb and TgAb of newly diagnosed hyperthyroid adult Isfahani population in comparison with control group in 2006

Parameter	Euthyroid (n=295)#	Subclinical hyperthyroid (n=15)	Overt hyperthyroid (n=6)	P value
T4*(µg/dl)	6.7 (3.8-11.6)	8.2 (5.1-11.8)	11.5 (9.4-18.7)	0.0001
TSH* (mU/L)	2.3 (0.5-4)	0.1 (0.05-0.29)	0.1 (0.05-0.2)	0.0001
T3 (ng/dl)	135.4 (17.6)	139.9 (33)	220.5 (42)	0.0001
T3RU (%)	33.7 (2.4)	34.2 (2.5)	36.3 (1.7)	0.03
FT4I	2.25 (0.4)	2.8 (0.68)	4.6 (1.3)	0.0001
TPOAb* (IU/mL)	5.4 (0-2270) (n=295)	2.7 (0.6-75) (n=12)	105 (1-1000) (n=10) £	0.04
TgAb* (IU/mL)	15.6 (0-8430) (n=295)	63 (0.1-2955) (n=12)	134 (2.7-1168) (n=10) £	0.1

T4, T3, T3RU and TSH were measured in 142 euthyroid participants whose blood sample was taken for the 2nd time. However, TPOAb and TPOAb were measured in 153 more euthyroid people on their stored serum samples.
&P value: Overt hyperthyroidism vs. euthyroid people.
*Data were not distributed normally
£ Including 4 out of 5 patients who were on methimazole

reason is probably iodine sufficiency of the studied population (median UIC is 18 µg/dl in general population). However, there is no discrepancy between our study with what was previously reported (27, 28). Iran is a country with young population. The age distribution in our studied population is similar to other parts of Iran (29), which can explain why older people entered our study with less frequency (Fig.1).

We found that hyperthyroidism is relatively similar to that reported by studies in iodine sufficient areas (5, 9) and our study can be compared with several other population based studies.The limitation of this study was that we had not any information about the prevalence of overt and subclinical hyperthyroidism in the Isfahani population before the start of universal prophylaxis. In a study in Tehran Heydarian et al evaluated the prevalence of thyroid abnormalities before and after national salt iodization in Tehrani adults, according to their reports Overt and subclinical hyperthyroidism was detected in 4.4 and 4.4/1000 in 1983-1984 vs 0.7 and 5.6/1000 in 1999-2000, respectively. They concluded that salt iodization resulted in adequate UIC, decrease in serum TSH and subclinical hyperthyroidism in men, and an increase in thyroid autoantibodies without significant change in thyroid abnormalities. Benefits of iodine supplementation far outweigh its hazards in Tehrani adults (20).

In National Health and Nutrition Examination Survey 1988-1994 (NHANES III), a large population-wide study in the USA, hyperthyroidism was found in 1.3%

Table 3. The prevalence of thyroid autoantibody positivity in hyperthyroid and euthyroid people in Isfahan, 2006

Thyroid status	Only TPOAb n (%)	Only TgAb n (%)	TPOAb & TgAb n (%)	TPOAb & TgAb n (%)	TPOAb and/or TgAb n (%)
Hyperthyroid (n=22) #	3(25%)	6 (50%)	3(25%)	3(25%)	12* (54.5%)
Women (n=15)	1	4	2	2	7
Men (n=7)	2	2	1	1	5
Euthyroid (n=295) $	25(29.1%)	32(37.2%)	29(33.7%)	29(33.7%)	86(29.2%)
Women (n=210)	18	30	20	20	68**
Men (n=85)	7	2	9	9	18

In 22 out of 46 hyperthyroid people, autoantibodies were measured, including 4 out of 5 patients who were on methimazole.
$In 295 out of 2254 euthyroid adult Isfahani people, autoantibodies were measured.
* P<0.05 hyperthyroid vs. euthyroid people and ** P<0.05 female vs male

(0.5% overt and 0.7% subclinical) of the total population (5). Volzke et al, in their study in Germany, in a previously iodine deficient area, have reported a prevalence of 1.8% for subclinical and 0.4% for overt hyperthyroidism (9). Hoogendoorn et al. in their study in Nijmegen, the Netherlands, have reported that overt and subclinical hyperthyroidism was found in 0.4% and 0.8% of the total population (30). In the Whickham survey performed in the UK at a time when no sensitive TSH assay was available, hyperthyroidism was found in 1.6% of participants (31).

Comparing our results with the results of a similar study in Tehran, Iran, by Heydarian et al. the prevalence of two subtypes of hyperthyroidism was higher in our study. They reported no new cases of overt hyperthyroidism and a rate of 4.2/1000 for subclinical hyperthyroidism, a decade after salt iodization program (15). The research of Heydarian et al was done only in the East of Tehran. However, we studied the population of Isfahan from all parts of the city. This may be the reason for the difference in these two populations. The higher prevalence of the disease in women was similar to our study. As the design of our study was relatively similar to that research, the higher prevalence of hyperthyroidism in our study may be due to factors such as high rate of autoimmunity or other related environmental factors, which will be reported later.

The prevalence of overt and subclinical forms of hyperthyroidism was 0.1% and 0.34%, respectively, in the Busselton thyroid study in Australia (1966-1981) (32).

The higher rate of hyperthyroidism in women than men, in our study was similar to many other studies in this field (4, 5, 15, 32). In the Health Study of Nord-Trondelag (HUNT) in Norway in 2000, 0.6% of men and 2.5% of women reported to have hyperthyroidism (4). There was not similar relation for the subclinical subtypes of hyperthyroidism in our study. It may be due to small sample size of our hyperthyroid patient, which could explain also the lack of relation between hyperthyroidism and increasing age. However, for more accurate conclusions more studies are needed in this field.

Median of UIC in this study was in appropriate range and prevalence of hyperthyroidism was not different in groups with iodine deficiency, sufficiency and excess. Although iodine excess was observed in 18.7% of participants, it was not any relation between hyperthyroidism and iodine excess in the present study.

Both low and high iodine intake of a population are associated with an increase rate of thyroid abnormalities and the consequences are more severe for iodine deficiency than iodine excess (33, 34). According to many studies, mild and moderate iodine deficiency is associated with a high incidence and prevalence of goiter and hyperthyroidism, whereas high iodine intake may enhance thyroid autoimmunity, leading to hypothyroidism (7, 11, 35). Pederson et al. in their study in Denmark compared the incidence of thyroid disease in areas with small differences in iodine intake and they concluded that the incidence rate of overt hyperthyroidism was much higher in the population with moderate iodine deficiency than in area with mild iodine deficiency (36). Laurberg et al. in a comparative epidemiological study have determined the prevalence of thyroid abnormalities in two regions with low (Jutland) and high (Iceland) iodine intake and they indicated that thyroid dysfunctions in the population with low or high iodine intake develop in opposite direction: hyperthyroidism and goiter when iodine intake is relatively low and thyroid hypofunction when iodine intake is relatively high (37). Our region is an iodine repleted area, so present findings are in accordance with mentioned factors and 15 years are sufficient enough to reduce the effect of iodine deficiency on thyroid gland.

On the other hand, some studies have reported an increased incidence of hyperthyroidism after the increment in iodine intake due to the occurrence of iodine induced hyperthyroidism (38-40). Our findings showed that iodine intake does not change the prevalence of hyperthyroidism and also Haydarian et al. have indicated similar results in this field in Tehran (15). The results of current study were also in accordance with the study of Yang et al. in China, which investigates the prevalence of hyperthyroidism in three areas with borderline iodine deficiency, mild iodine excess and severe iodine excess. They reported that the incidence of hyperthyroidism did not significantly increase after the introduction of universal salt iodization (41). Lack of relation between thyroid hyperfunction and iodine supplementation in our study may be due to the fact that it was performed fifteen years after implementation of iodine prophylaxis and we have reached a sustained phase in this field. However, according to a recent study in Poland, which assessed the prevalence of hyperthyroidism just after iodine supplementation, rising in iodine

intake after implementation of iodine prophylaxis in an area with iodine deficiency may lead to an increase in thyroid autoimmunity and prevalence of hyperthyroidism. They concluded that observed increasing rate of hyperthyroidism is possibly the early side effect of iodization and is a temporary process (42). In another study in Turkey, which evaluated the effect of iodine intake on the prevalence of thyroid dysfunction and autoimmunity after two years of iodization in two regions with different iodine status, hyperthyroidism and autoimmunity were significantly higher in an iodine sufficient area than in iodine deficient ones (43), but as mentioned earlier their study was done two years after iodization and it seems that the temporary effect of iodination still remains.

The presence of thyroid autoantibodies indicates an autoimmune thyroid disease component that may lead to the development of thyroid dysfunction. In the present study, TgAb and TPOAb or TgAb were more prevalent in hyperthyroid patients than euthyroid ones with similar results for TPOAb, whereas it seems that TPOAb is a more useful marker for thyroid autoimmunity (5, 44, 45). It may be due to our small sample size of hyperthyroid patients evaluated for autoantibodies or as reported by Laurberg et al. both TPOAb and TgAb in the serum are mainly markers and not inducers of disease and can result from different abnormalities. The major event in autoimmunity would be lymphocytic infiltration of the gland and thyroid antibody formation would be a secondary phenomenon (37). There is another opinion that iodine allows a slight increase of circulating thyroid antibodies, but this does not mean an increase of autoimmune thyroid diseases. However, more studies during longer time are needed for a more accurate conclusion in this field.

CONCLUSION

Comparing epidemiological studies of thyroid dysfunction and thyroid autoantibodies is difficult. It is mostly due to the differences in genetic background and environmental factors such as iodine intake. It may also be explained by different biochemical, clinical and epidemiological methods, which have been applied, especially for thyroid autoantibodies. There is no international standardization of the assays for antithyroid antibodies and there are different cut-off values (46). However, the rate of hyperthyroidism in our region was in the range considered for iodine sufficient areas and thyroid autoantibodies may have a role, which needs further studies.

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