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The role of thyroid autoantibodies in the etiology of endemic goiter in schoolchildren of Isfahan, Iran

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ABSTRACT. ***Background:*** **Eleven years after the initiation of universal salt iodization program in Iran, the prevalence of goiter is still high in some areas.** ***Aim:*** **To investigate the role of thyroid autoimmunity in the etiology of residual goiter in schoolchildren of Isfahan, Iran.** ***Material and methods:*** **In a cross-sectional study, 2331 schoolchildren were selected by multi-stage random cluster sampling. Thyroid size was estimated in each child by inspection and palpation. Urinary iodine concentration (UIC), serum anti-thyroperoxidase antibody (anti-TPO Ab), and anti-thyroglobulin antibody (Anti-Tg Ab) were measured.** ***Results:*** **Overall, 32.9% of children had goiter. The median UIC was 1955.5 µg/dl. There was significant difference in prevalence of positive anti-TPO Ab in goitrous (grade 2) and non-goitrous children (9.7 *vs* 3.7%, p= 0.02). Goitrous children had higher prevalence of positive anti-Tg Ab than non-goitrous ones (15.1 *vs* 3.1%, p<0.001).** ***Conclusions:*** **According to the present study, goiter is still a public health problem in this region. This study suggests that thyroid autoimmunity is among the contributors of goiter persistence after elimination of iodine deficiency in Isfahan.**
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INTRODUCTION

Iodine deficiency (ID) is recognized as the major preventable public health worldwide problem. It is estimated that 750 million people worldwide are at risk of ID disorders (IDD) (1). IDD can be presented with a wide variety of clinical manifestations ranging from congenital anomalies, cretinism, deaf mutism, psychomotor defects to severe goiter.

The relationships between dietary iodine intake, endemic goiter and prevalence of clinical or subclinical thyroid autoimmunity are controversial (2). In Greece, cases of Hashimoto's thyroiditis were reported after salt iodization (3). In other studies, the prevalence of thyroid autoantibodies is reported to be between zero to 61.6% (4-6). In China, only a few children had high levels of antithyroid antibodies after iodine replenishment (7) whereas high prevalence of positive antithyroid antibodies was found in Sri Lankan children after iodine supplementation (8).

Due to the high prevalence of goiter in Iran, the Iranian National Committee for control of IDD was established in 1988. Salt iodization started in 1990, but was not mandatory until 1994. Isfahan, the second largest city of Iran, locates in central part of the country with an approximate population of 2,000,000. The prevalence of goiter in Isfahan had been estimated to be 92% in girls and 85% in boys in 1989 (9). According to another study that was conducted in 1997 the prevalence of goiter among Isfahan 6-18-yr-old-children was estimated to be 62% (10).

The present study was carried out to estimate the goiter prevalence and iodine status and investigate the role of thyroid autoantibodies as a possible contributor of endemic goiter in Isfahan schoolchildren, 11 yr after the initiation of the mandatory universal salt iodization program in Iran.

MATERIAL AND METHODS

This was a cross sectional study performed on schoolchildren of Isfahan in 2005. Subjects were enrolled with a multistage cluster random sampling. Goiter grading was performed by two endocrinologists according to World Health Organization (WHO)/United Nations Children's Fund (UNICEF)/International Council for the Control of Iodine Deficiency Disorders (ICCIDD) criteria (1).

Urine iodine concentration (UIC) was measured by the digestion method based on a modification of Sandell-Kolthoff reaction (1, 11). Serum T_4 was measured with radioimmunoassay (Iran Kavoshyar Co., Tehran, Iran). Serum TSH concentration was determined using immunoradiometric assay (Iran Kavoshyar Co., Tehran, Iran). The normal range for T_4 was 4.5-12 µg/dl and for TSH was 0.3-3.9 mIU/l. Serum anti-thyroglobulin antibody (anti-Tg Ab) and anti-thyroperoxidase antibody (anti-TPO Ab) were measured by Rapid enzyme-linked immunosorbent assay (ELISA) (Genesis Diagnostics, Littleport, UK). Anti-Tg Ab and anti-TPO Ab concentrations above100 IU/ml and 75 IU/ml, respectively, were considered positive.

Quantitative variables are presented as mean±SD. Independent sample t-test was used to compare normally distributed data in different groups. Parameters not normally distributed were compared by Mann-Whitney test. Prevalence of positive anti-thyroid antibodies between goitrous and normal children was compared by Chi-square test. Correlation between quantitative variables was calculated by Pearson correlation coefficient. A p-value <0.05 was considered statistically significant. All analysis was performed using SPSS version 15 (SPPS Corp, Chicago, IL, USA). Written consent was obtained from all children's parents who

Key-words: Autoimmune thyroid disease, goiter, iodine deficiency, Iran.

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Table 1 - *Thyroid size determined by inspection and palpation in schoolchildren of Isfahan, Iran.*

		Thyroid size		
	No.	Grade 0	Grade 1	Grade 2
Boys	898	66.3%	27.3%	6.4%
Girls	1433	67.6%	29.0%	3.4%
All	2331	67.1%	28.3%	4.6%

were informed about the study. The study was approved by the Ethics Committee of the Isfahan Endocrine and Metabolism Research Center affiliated to Isfahan University of Medical Sciences.

RESULTS

Two thousand three hundred and thirty-one 6 to 13-yr-old schoolchildren were enrolled in this study with female:male ratio of 1.60. The mean age±SD was 9.39±1.18 for girls and 9.47±1.12 for boys. Overall 32.9% of subjects were classified as goitrous (Table 1). While goiter prevalence among girls was 32.4%, 33.7% of boys were goitrous (p=0.51).

UIC was measured in 454 schoolchildren. The mean±SD and median UIC was 220.66±17.33 and 195.50 µg/l, respectively; 15.8% of total samples had iodine excretion level below 100 µg/l and 3.7% had iodine level below 50 µg/l; 25.6% of subjects had UIC between 200 and 300 µg/l and 23.8% had UIC more than 300 µg/l. UIC in goitrous and non-goitrous children was 220.91±119.44 and 220.16±114.64 µg/l, respectively (p=0.57).

Serum anti-Tg Ab and anti-TPO Ab were measured in 93 goitrous (grade 2) and 326 non-goitrous children. The mean±SD of thyroid autoantibodies in children with and without goiter is presented in Table 2. Although goitrous children had higher levels of serum anti-Tg Ab and anti-TPO Ab than non-goitrous ones, the difference was not statistically significant (Table 2).

Positive anti-Tg Ab was found in 22 schoolchildren, resulting in a total prevalence of 5.3%. Boys had higher prevalence of positive anti-Tg Ab than girls did (7.5 *vs* 3.2%, p=0.05). The prevalence of subjects with positive anti-Tg Ab in goitrous and non-goitrous children was 15.1 and 3.1%, respectively [odds ratio: 4.67, 95% confidence interval (CI): 1.95-11.19, p<0.001]. Goitrous boys had higher prevalence of positive anti-Tg Ab than non-goitrous boys did (18 *vs* 4.7%, p=0.003). Girls with goiter had higher prevalence of positive anti-Tg Ab than non-goitrous girls did (11.6 *vs* 1.7%, p=0.002).

Positive anti-TPO Ab was found in 21 schoolchildren, resulting in a total prevalence of 5%. Boys had higher prevalence of positive anti-TPO Ab than girls did (6.5 *vs* 3.6%, p=0.17). The prevalence of subjects with positive anti-TPO Ab in goitrous and non-goitrous children was 9.7 and 3.7%, respectively (odds ratio: 2.80, 95% CI: 1.14-6.88, p=0.02).

Twenty-nine children (6.9%) were positive for at least one of the anti-thyroid antibodies. Whilst 15.1% of goitrous children had positive anti-thyroid antibodies, 4.6% of non-goitrous children had positive anti-thyroid antibodies (odds ratio: 3.67, 95% CI: 1.70-7.93, p<0.001).

Goitrous children had significantly lower T_4 levels than non-goitrous ones (8.20±1.66 *vs* 8.84±1.48 µg/dl, p<0.001). There was not any significant difference between TSH level in goitrous and non-goitrous children (3.58±5.11 *vs* 2.65±1.36 mIU/l, p=0.09). Whilst mean serum TSH in children with positive and negative anti-Tg Ab did not differ significantly, it was significantly higher in children with positive anti-TPO Ab than children with negative anti-TPO Ab (4.35±2.97 *vs* 2.78±2.68 mIU/l, p=0.004). On the other hand, while children with positive anti-Tg Ab had significantly lower T_4 level than negative children did (7.94±1.79 *vs* 8.74±1.52 µg/dl, p=0.04), T_4 level in subjects with positive and negative anti-TPO Ab did not differ significantly.

There was no child with overt hypothyroidism and about 18% of children had subclinical hypothyroidism. The prevalence of subclinical hypothyroidism in subjects with positive anti-TPO Ab was higher than subjects with normal anti-TPO Ab level did (42.9 *vs* 16.7%, p=0.002). In addition, children with positive anti-Tg Ab had higher prevalence of subclinical hypothyroidism than children with normal anti-Tg Ab levels did (33.3 *vs* 17.1%, p=0.04).

Serum TSH was correlated with anti-TPO Ab (r=0.11, p=0.02) and anti-Tg Ab (r=0.18, p<0.001). Serum T_4 had a negative correlation with anti-Tg Ab (r=–0.16, p=0.001).

DISCUSSION

According to the present study goiter prevalence in Isfahan has decreased from about 89% in 1989 (9) and 62% in 1997 (10) to 32.9% in 2005. This implies ID has been the most important cause of endemic goiter and shows the effective role of the mandatory universal salt iodization program started in 1994, in treating goiter. However, goiter is still endemic in this iodine replenished area and a

Table 2 - *Serum anti-thyroperoxidase antibody (anti-TPO Ab) and anti-thyroglobulin antibody (Anti-Tg Ab) in schoolchildren of Isfahan, Iran.*

		Goitrous	Non-goitrous	p
Boys (no.=199)	Anti-Tg Ab (IU/ml)	145.44 (442.73)	30.90 (107.50)	0.08
	Anti-TPO Ab (IU/ml)	60.52 (156.70)	29.92 (119.21)	0.21
Girls (no.=219)	Anti-Tg Ab (IU/ml)	129.10 (631.46)	38.27 (276.26)	0.36
	Anti-TPO Ab (IU/ml)	54.59 (181.22)	16.70 (83.75)	0.19
Total (no.=418)	Anti-Tg Ab (IU/ml)	137.88 (535.25)	34.90 (215.67)	0.06
	Anti-TPO Ab (IU/ml)	57.78 (167.57)	22.74 (101.55)	0.07

Data presented as mean (SD).

severe public health problem in this region according to WHO/UNICEF/ICCIDD recommended criteria (1).
According to WHO/UNICEF/ICCIDD recommended criteria, the indicator of ID elimination is a median value for UIC of 100 µg/l, and UIC should not be below 50 µg/l in more than 20% of samples (1). In the studied population, the median UIC was 195.5 µg/l and 3.7% of the population had UIC below 50 µg/l. It means there is no biochemical ID or no inadequacy in iodine intake of the overall population.
We have recently showed the role of selenium deficiency in the persistence of goiter in Isfahan schoolchildren (12). However, the role of vitamin A deficiency was ruled out in these children (13). In the present study, we tried to investigate the role of thyroid autoantibodies in the etiology of persistent goiter in Isfahan.
In the present study, we found a higher prevalence of thyroid autoantibodies in goitrous children than nongoitrous ones and thyroid autoimmunity was associated with a 3.67-time increase in the risk of goiter. Although thyroid autoimmunity did not play a key role in the pathogenesis of endemic goiter in Poland (14), more than half of goitrous schoolchildren in Greece and Iran presented with positive thyroid autoantibodies (15, 16). In a recent study in Isfahan women, Aminorroaya et al. revealed an association between thyroid autoimmunity and pathogenesis of some common thyroid disorders such as goiter (17).
As stated, 5% of subjects in this study had high levels of anti-TPO Ab. Studies conducted in Morocco, Germany and Sardinia, reported that only 1%, 3.4%, and 2.9% of children had elevated anti-TPO Ab (18-20). The prevalence of elevated anti-TPO Ab was 7% in Sweden schoolchildren (21). In a study in Greece (22) 10.6% of schoolchildren had positive anti-TPO Ab/Tg Ab that was higher than that in our study (6.4%). Given that positive antibody may increase with age (22), the difference between the prevalence of thyroid antibodies may be due to the younger age of our subjects than that of the Greek students. The prevalence of positive anti-TPO Ab/Tg Ab in the schoolchildren of Semirom (a city near Isfahan) was reported to be 7.3% (2).
In the present study, positive thyroid antibodies were present more in boys than girls. This is similar to a previous study in Semirom (2) and in contrast with another study in Germany in which females had 2.7 times higher prevalence of high anti-TPO Ab than males (19).
Discrepant results have been reported in different areas of the world regarding the association between iodine supplementation and anti-thyroid autoantibodies. In published studies in Morocco (18) and Romania (23), anti-thyroid antibodies did not change after iodine supplementation. On the other hand, Markou et al. and Heydarian et al. reported a significant increase in the thyroid autoantibodies after iodine supplementation in Azerbaijan and Iran (24, 25). Since there is not any data about the levels of thyroid antibodies in Isfahan prior to the universal iodine supplementation in Iran, we cannot make any comparison to find the effect of this program on the levels of thyroid autoantibodies.
According to WHO/UNICEF/ICCIDD criteria, 25.6% and 23.8% of subjects in our study had iodine intake more than adequate and excessive iodine intake, respectively. Wide variation in iodine concentrations and a high proportion of commercial salt samples with excessive iodine is worrying in view of possible iodine induced immune phenomena (26). We strongly suggest performing studies to analyze the iodine content of commercially available salt samples in Isfahan.
In our study, about 37% of the students with abnormal thyroid autoantibodies had subclinical hypothyroidism. This is in contrast to a study in Morocco in which no child with elevated TPO-Ab had abnormal TSH or T_4 concentrations (18). In Sardinian and Sri Lankan studies, about 1% of children showed borderline to slightly increased serum TSH, which was found in children with positive anti-thyroid antibodies (20, 27). In those studies, the prevalence of subclinical hypothyroidism was lower than our study. Other studies have also reported low rates of subclinical hypothyroidism or hyperthyroidism in schoolchildren with thyroid autoimmunity (28, 29). Rezvanfar et al. reported that >30% of goitrous children with positive anti-TPO Ab had subclinical or overt hypothyroidism (30).
It should also be mentioned that, in the present study, goitrous children with positive thyroid autoantibodies could be cases of Hashimoto's thyroiditis and those with elevated TSH might benefit from T_4 treatment.
The main limitation of our study was classification of the participants into goitrous and non-goitrous groups by inspection and palpation. Classification of subjects into different goiter groups could be more accurate if we used thyroid ultrasonography instead of inspection and palpation.
In conclusion, goiter is still a public health problem in Isfahan. ID alone cannot explain the still high prevalence of goiter in this region. Thyroid autoimmunity can be considered as a contributor of goiter in this city. There might be a linkage between excessive iodine intake and thyroid autoimmunity in Isfahan schoolchildren.

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