Original Article

High prevalence of goiter in an iodine replete area: do thyroid auto-antibodies play a role?

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Introduction: Despite long standing iodine supplementation in Iran the prevalence of goiter remains high in some areas. This may suggest that causes other than iodine deficiency, such as autoimmune thyroid diseases, should also be considered. We therefore assessed the prevalence of anti-thyroid antibodies in children living in an inland area in Iran and correlated these findings with prevalence of goiter within this region.

Methods: In a cross-sectional study, 1948 students were selected by multistage random cluster sampling from the 108 primary schools (age, 7-13 year-old) of the urban and rural areas of Semirom. After obtaining written consent from their parents, the children were examined by endocrinologists for goiter grading. Grade 2 goitrous children (108 cases) were compared with non-goitrous children (111 children as control group) for anti-thyroid antibodies.

Results: Overall, 36.7% of 1948 students had goiter. The mean urinary iodine excretion level was 1.49±0.7 μmol/L. This was within normal limits. Of 219 children studied, 4.3% presented with subclinical hypothyroidism, and 7.3% had positive anti-thyroid antibodies. There was non-significant difference of positive thyroperoxidase antibody (anti-TPO) (Odds Ratio= 3.2, p= 0.13) but significant difference of anti Tg between goitrous and non goitrous children (Odds Ratio: 5.6, 95% CI: 1.18-26.0, p: 0.015).

Conclusion: This study suggests that autoimmunity may be one of the mechanisms responsible for goiter persistence after iodine replenishment in this iodine deficient region, but the role of other factors should also be considered.

Key Words: goiter, antithyroid antibody, thyroidperoxidase antibody, thyroglobulin antibody, autoimmune thyroid disease

INTRODUCTION

The prevalence and pattern of many thyroid disorders depend on ethnic and geographical factors especially iodine intake.[1] Virtually 750 million people worldwide are at risk of iodine deficiency disorders (IDDs) based on goiter prevalence.[2]

The consequences of persisting iodine deficiency are goiter, hyperavidity of the thyroid for iodide (which increases the risk of thyroid irradiation in the event of a nuclear accident) and subclinical hypothyroidism during pregnancy and early infancy (with a concomitant risk of minor brain damage and irreversible impairment of the neuropsychointellectual development of offspring.[3]

In response to a high prevalence of endemic goiter in some areas in Iran, reported as high as 89.5% in Semirom,[4] a national plan for controlling IDDs was initiated since 1989, and a national law of the mandatory salt iodization for household usage was passed in 1994.[5] Since then, the prevention of IDDs in Iran has been very successful.[5-7] Despite sufficient iodine intake, the prevalence of goiter is still high in some regions of Iran,[8;9] so causes other than iodine deficiency, such as autoimmune thyroid disease (AIT) have to be considered in children with goiter.[9]

The relationships between dietary iodine intake, endemic goiter and prevalence of clinical or subclinical thyroid autoimmunity are controversial. In Greece, cases of Hashimoto's thyroiditis were reported after salt iodization.[10] In other studies, the prevalence of thyroid autoantibodies are reported to be between zero to 61.6%.[11-13] In China, only a few children had high levels of antithyroid antibodies after iodine replenishment,[14] whereas high prevalence of positive antithyroid antibodies were found in Sri Lankan children after iodine supplementation.[15]

In 1993, all citizens of Semirom were given a single dose of intramuscular injection of 480 mg iodized oil.[4] The goiter prevalence did not decrease as expected (less than 5% until 2000) seven years after iodine injection and salt

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Manuscript received 24 January 2006. Initial review completed 22 March 2006. Revision accepted 24 October 2006.

iodization described as above, suggesting other factors than iodine deficiency may be responsible for persistence of goiter in that area.

Data on the prevalence of thyroperoxidase antibody (TPO Ab) and thyroglobulin antibody (Tg Ab) in Iranian children are limited, the present study was conducted to assess the prevalence of antithyroid antibodies and its correlation with goiter and thyroid dysfunction in children living in Semirom, Iran.

MATERIALS AND METHODS

This study was performed in Semirom, a mountainous region in the central area of Iran, where goiter was hyperendemic with a prevalence of about 89.5%, estimated in 1994 just before national mandatory salt iodization.[16]

This was a cross sectional, descriptive study performed on school children of Semirom.

Elementary schools n=108, with 4773 students were considered as primary sampling units, of which 79 schools were from rural areas with 2449 students (M/F: 1247/1202), and 29 schools from urban areas with 2324 students (M/F: 1126 /1198). By a multistage cluster sampling, 1948 students were selected randomly. Written consents were obtained from parents of children before recruitment to the study.

Children with history of exposure to radioactive iodine, thyroid surgery or significant underlying disease such as cardiopulmonary, liver or renal problems were excluded. Information for exclusion was collected based on available medical records of students and interviews with parents, teachers and participants.

Endocrinologists examined all children and goiter grading was performed according to WHO classification in 3 groups (grades 0, 1 and 2).[2]

The first group (grade 0) was considered as having normal thyroid size (control group) in comparison with others who had goiter (grades 1 and 2). The sum of grades 1 and 2 provided the total goiter rate (TGR) of the study population.

To investigate responsible factors for goiter, grade two goitrous children were compared with equal number of randomly selected children from control group for serum anti TPO, anti Tg, thyroxine (T4), thyroid stimulating hormone (TSH) and urinary iodine concentration.

The blood samples were transported on dry ice to reference laboratory of Isfahan Endocrine and Metabolism Research Center. The samples were stored at -70 ^{o}C until analysis.

All urine and blood analysis were performed within 26 hours of sampling by one expert person.

Urinary iodine concentration (UIC) was measured by digestion method based on a modification of Sandell-Kolthoff reaction[2,17] (Intra-assay CV 1.2% and inter-assay CV 2.2%). Concentrations less than 0.77 µmol/L were considered as iodine deficiency.[2]

Serum T4 concentrations were measured with radioimmunoassay (RIA) by Iran Kavoshyar kits (Tehran, Iran) (Intra-assay CV 4.7% and inter-assay CV 4.9%). Normal range for T4 level was 58-154 nmol/L. Serum TSH concentrations were assayed with IRMA by Iran Kavoshyar kits (Intra-assay CV 1.5% and inter-assay CV 1.9%). Normal range for TSH level was 0.3-3.9 mIU/L.

Anti Tg and anti TPO were measured by Rapid ELISA (Genesis Diagnosis Co,). Intra and inter-assay CV for anti Tg was <12% and for anti TPO were 7% and 5%, respectively. Anti Tg and Anti TPO concentrations more than 100 IU/mL and 75 IU/mL, respectively, were considered positive.

The study was approved by the ethics committee of Goiter Research Center affiliated to Isfahan University of Medical Sciences. Written permission was taken from the Provincial and local Organization of Education.

Statistical analysis

Variables with normal distribution (serum T4 and TSH) are presented as mean (SD). Prevalence of positive antithyroid antibodies between goitrous and normal children was compared by Chi-square test. The comparison of positive anti Tg or anti TPO antibodies between three groups euthyroid, subclinical hypothyroid and overt hypothyroid were also performed by Chi-square test.

Correlation between quantitative variables was calculated by Pearson correlation coefficient. Exact *p*-values were reported and *p*-values less than 0.05 were considered statistically significant. Analyses were performed with SPSS statistical package version 11.5 Chicago, IL, USA.

RESULTS

Overall 1948 students were enrolled in this study, 1012 were male and 936 were female (male to female ratio was 1.08). Their age ranged seven to 13 years (mean 9.3 years) (Table 1).

1828 school children (879 from urban and 949 from rural areas) were examined for goiter staging. Of these, 1158 were classified as having goiter grade 0 (63.3%), 555 had goiter grade 1 (30.4%) and 115 had goiter grade 2 (6.3%) with total goiter prevalence of 36.7%.

The mean UIC in children was 1.49±0.7µmol/L. Mild (UIC<0.77µmol/L) and moderate (UIC<0.38µmol/L) iodine deficiency were detected in 6.4% and 3.2% of students, respectively. Only 1.8% of children were severely iodine deficient (UIC<0.154µmol/L).

Goiter prevalence was not statistically different between boys and girls (*p*: 0.06).

Grade 2 goitrous children, n=114 and equal number of

Table1. Baseline characteristics of Semirom school children, Iran, 2003

		Mean Age	non goitrous n (%)	goiter stage1 n (%)	goiter stage2 n (%)	Total n
Sex	Male	9.35	643 (65.0%)	289 (29.2%)	57 (5.8%)	989
	Female	9.31	515 (61.4%)	266 (31.7%)	58 (6.9%)	839
	Total	9.33	1158 (63.3%)	555 (30.4%)	115 (6.3%)	1828

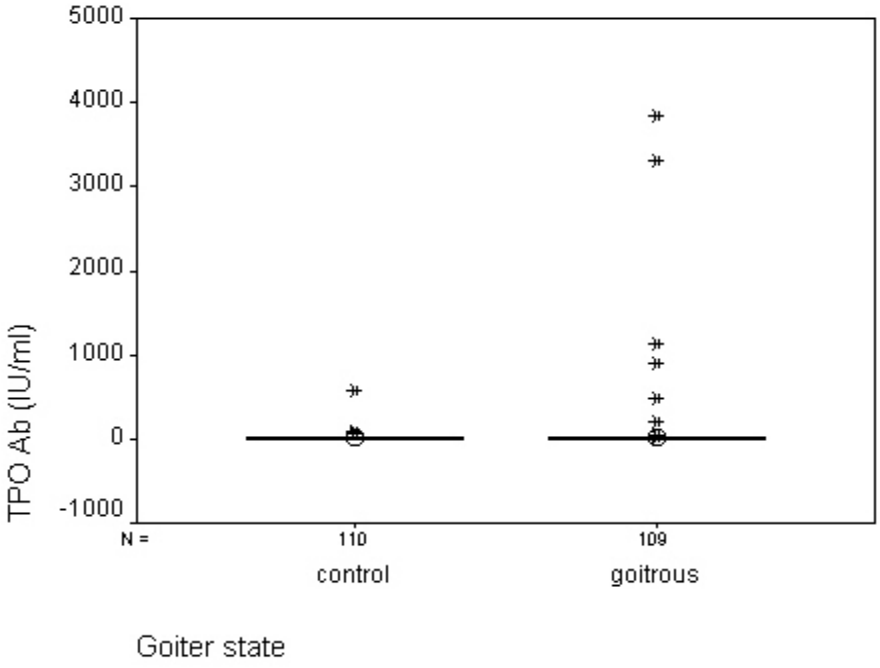

Figure 1. TPO antibody in normal and goitrous children

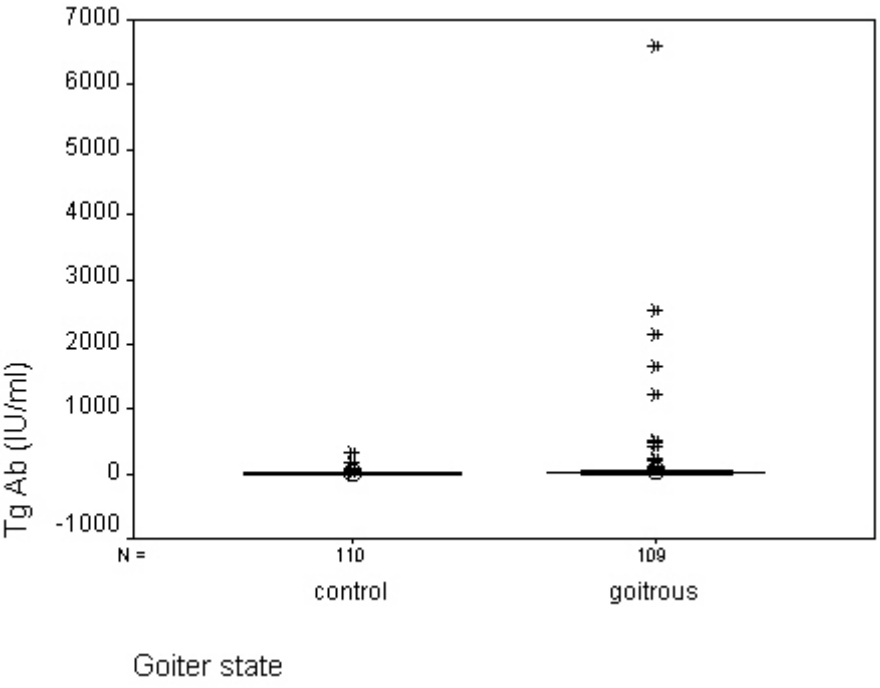

Figure2. Tg antibody in normal and goitrous children

randomly selected children from control group agreed to enrolment in this sub- study of anti-thyroid antibody evaluation.

Anti-thyroid antibodies were measured in 219 children, 111 children had no goiter (control group) and 108 had goiter grade 2 (case group).

There was no difference of positive anti TPO between two genders (*p*: 0.423) and also goitrous and non goitrous children (*p*=0.13) (Fig 1). On the other hand, positive anti Tg was significantly different between two genders (*p*=0.004) and goitrous and non goitrous children (Fig 2) (Odds Ratio: 5.6, 95% CI: 1.18-26.0, *p*=0.02,) (Table 2).

Sixteen out of 219 children (7.3%) (4 females and 12 males) were positive for at least one of anti-thyroid antibodies (*p*=0.05). Of these, 4 children were non-goitrous and 12 were goitrous (Odds Ratio: 3.34, 95% CI: 1.04-10.71, *p*=0.03).

There was significant differences between serum T4 concentration (*p*=0.04), but no differences in serum TSH concentration (*p*=0.07), in goitrous and non-goitrous children (Table 3).

There was a significant positive correlation of serum TSH and anti Tg (r=0.28, *p*=0.001) and with anti TPO (r=0.14, *p*=0.05).

Table2. Anti thyroid antibody state in Semirom school children, Iran, 2003

	Negative anti TPO n (%)	Positive anti TPO n (%)	Negative anti Tg n (%)	Positive anti Tg n (%)
Male(n=116)	111 (95.7%)	5 (4.3%)	105 (90.5%)	11 (9.5%)
Female(104)	101 (97.1%)	3 (2.9%)	103 (99.0%)	1 (1.0%)
p		0.423		0.004
Non goitrous (n=111)	109 (98.2%)	2 (1.8%)	109 (98.2%)	2 (1.8%)
Goitrous stage2 (n=108)	102 (94.4%)	6 (5.6%)	98 (90.7%)	10 (9.3%)
p		0.131		0.015

Table3. Mean serum TSH, T4 and urine iodine in Semirom school children

Sex	Goiter state	TSH (mIU/L) Mean (SD)	T4 (nmol/L) Mean (SD)	Urine Iodine(µmol/L) Mean (SD)
Male	non goitrous	2.59 (1.31)	120 (18.5)	1.50 (0.686)
	goitrous stage2	3.24 (3.85)	111 (17.1)	1.56 (0.736)
	Total	2.87 (2.70)	116 (18.3)	1.51 (0.684)
Female	non goitrous	2.32 (1.02)	115 (19.7)	1.40 (0.831)
	goitrous stage2	2.87 (1.78)	113 (23.0)	1.74 (0.609)
	Total	2.60 (1.48)	113 (21.4)	1.46 (0.802)
Total	non goitrous	2.47 (1.19)	118 (19.2)	1.45 (0.757)
	goitrous stage2	3.04 (2.92)	112 (20.5)	1.66 (0.648)
	Total	2.74 (2.19)	115 (19.9)	1.48 (0.741)

Serum anti TPO significantly correlated inversely with serum T4 concentration (r=-0.18, *p*=0.010).

Mean serum TSH and T4 in negative and positive anti-thyroid antibody children were 2.58±1.96 and 5.13±3.73 mIU/L, (*p*=0.001) and 116±19.1 and 104±27.1 nmol/L, (*p*= 0.03), respectively.

Nine children (2 non goitrous and 7 goitrous, 5 males and 4 females) had sub-clinical hypothyroidism. Three children (all goitrous, 2 males and 1 female) had overt hypothyroidism. The prevalence of positive anti TPO and anti Tg was significantly different between 3 groups of euthyroid, subclinical and clinical hypothyroid children (*p*= 0.002 and 0.02, respectively).

Two male children had clinical and 4 students (3 females and one male) had subclinical hyperthyroidism.

DISCUSSION

As stated, we have shown that goiter prevalence has decreased from 89.5% in 1994 to about 36% in 2003. This implies iodine deficiency has been the most important cause of endemic goiter and also shows the effective role of a single intramuscular injection of iodized oil and salt iodization in treating goiter. However goiter is still endemic in this iodine- replenished area, and although iodine deficiency is still present in mild to moderate degrees, it cannot truly explain the yet high prevalence of goiter. Other explanations for this unexpected high goiter rate are the role of unknown goitrogens, autoimmunity, or other micronutrient deficiencies. This confirms that the role of other predisposing factors like autoimmune phenomena should be considered.

The prevalence of goiter in this area was similar to a study conducted in Tehrani students,[18] but was lower than our previous study in Isfahan.[9] The goiter prevalence rate found in our study was similar to that of India.[19]

The frequency of positive anti-thyroid antibodies is different between goitrous and non-goitrous children. This may explain a mechanism for goiter persistence after adequate iodine supplementation.

The expected correlations of these antibodies with serum TSH and T4 confirm that such results are not coincidental, but points to important clinical and epidemiologic findings.

Two hypotheses may explain the observed frequency of anti-thyroid antibodies in this study. First, this may be related to background prevalence of thyroid autoimmunity in the area. Second, thyroid autoimmunity may be a consequence of iodine supplementation.

Regarding the first theory, studies conducted in Morocco ,Germany and Sardinia, have shown that only 1%, 3.4% and 2.9% of children had elevated TPO-Ab.[20-22] In different studies performed in Sweden, Tuscany(Italy) and Sri Lanka, the percentage of TPO-Ab in school children was 7%, 4.3% and 10% respectively.[23-25] Similar prevalence of anti-thyroid antibodies has been reported in children living in endemic and non-endemic areas.[26;27] In a study in Greece, 10% of school children had positive TPO-Ab/Tg-Ab that was higher than in our study. Given that positive antibody may increase with age,[28] the difference between the prevalence of thyroid antibodies may be due to the younger age of our subjects than that of the Greek students. In some studies, despite lower prevalence of goiter, the frequency of TPO-Ab was similar to the present study.[29]

Regarding the second theory, discrepant results have been reported in different areas of the world. In published

studies in morocco,[20] and Romania,[30] anti-thyroid antibodies did not change after iodine supplementation, but Markou reported a significant increase in the thyroid auto antibodies 6 and 12 months after iodine supplementation in Azerbaijan.[31]

Iodinated thyroglobulin is responsible for triggering the autoimmune process due to long-term immunomodulatory effects of iodine, as reported to occur in populations exposed to prolonged iodine supplementation.[32] This remains a researchable area in our population. In our study, the prevalence of anti-thyroid antibodies was borderline significantly different between boys and girls; the difference between genders starts from the age of 11-12 years that implies the age and gender have important roles in thyroid autoimmunity,[33;34] and factors like sex hormones or gonadotropins might be involved. Different prevalence of goiter between pre-pubertal and adolescent children may be indirectly linked to these roles.

As only 12(11%) of the goitrous children were positive for anti-thyroid antibodies, autoimmunity can not explain most cases of endemic goiter in Iranian children. Factors like unknown goitrogens, protein-energy malnutrition,[35-37]Vitamin A,[38;39] Iron,[8]Selenium and Zn deficiencies[40;41] or their combination may be responsible causes.

The high prevalence of goiter could also be related to genetic background that is possibly due to a high degree of consanguinity in our community or to the influence of additional local environmental factors, which remain to be defined.

In most children studied, even those with positive anti-thyroid antibodies, thyroid function were normal. In our study, about 27.2% of the students with abnormal thyroid antibody had subclinical hypothyroidism that was in contrast to a study in Morocco in which no child with elevated TPO-Ab had abnormal TSH or T4 concentrations.[20] In Greece, the prevalence of subclinical hypothyroidism in school children was compatible to the present study, but just in spite of our findings, all students with subclinical hypothyroidism had positive anti-thyroid antibodies.[28] Similar findings have been published previously about thyroid function, based on TSH.[42] In Sardinian and Sri Lankan studies, about 1% of children showed borderline to slightly increased serum TSH, that was found in children with positive anti-thyroid antibodies.[23;43] In those studies the prevalence of subclinical hypothyroidism was lower than in our study. Other studies have also reported low rates of subclinical hypothyroidism or hyperthyroidism in school children.[44;45] The cause of this difference remains to be found, but we suggest that unknown local environmental factors in our community may have a role.

In the present study, anti-thyroid antibodies were linked to goiter prevalence and thyroid dysfunction; but most goitrous children were antibody negative, this finding is in line with studies conducted in Sardinia and Azerbaijan.[23;31]

We found significant difference in the mean serum TSH between children with positive and negative anti-thyroid antibodies. Our findings are consistent with some [46-48] but not with other studies conducted in iodine- replete areas, in which anti-thyroid antibodies were negative in all schoolchildren with subclinical hypothyroidism, but for minority of them.[31;49]

Anti-thyroid antibodies display geographical heterogeneity, which in some studies seems to be unrelated to goiter prevalence and/or to iodine supply or thyroid function.[23] Longitudinal studies are needed to assess whether these antibody positive children would suffer from clinical hypothyroidism in the future or not.

Few participants of our study had clinical and subclinical hyperthyroidism. It was reported that, after prophylaxis with iodine salt in Zaire, 14% of patients had undetectable serum TSH values.[50] Severe thyrotoxicosis also occurred in Zimbabwe after introduction of iodized salt.[51] According to previous studies, 2-6% of Azerbaijan's school children and 9% of rural students of Tehran had subclinical hyperthyroidism.[31;52] This difference can be due to acute high dose administration of iodized oil, prolonged goiter, older age, or some unknown mechanisms. The prevalence of goiter and subclinical hyperthyroidism in Ethiopian children was nearly similar to our study (43.6%.vs 36.7% and 0.8% vs. 0.6%).[53]

CONCLUSION

We concluded that autoimmunity may be one of the mechanisms responsible for goiter persistence after iodine replenishment in iodine deficient areas in Iran, but the role of other responsible factors should be investigated.

ACKNOWLEDGEMENTS

This study was funded by the Bureau for Research, Isfahan University of Medical Sciences. The authors are thankful from the authorities of the Provincial and local Education offices, and all the staff working with the project, students and their parents who had full cooperation.

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Original Article

High prevalence of goiter in an iodine replete area: do thyroid auto-antibodies play a role?

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碘充足的地區的高甲狀腺腫盛行率：甲狀腺自體抗體是否扮演一個角色?

前言：儘管伊朗長期補充碘，但在某些地區的甲狀腺腫盛行率仍然相當高。這個現象指出除了碘缺乏以外的原因，像是自體免疫疾病也應該被考慮。我們因此評估居住在伊朗內陸地區的孩童抗甲狀腺抗體的盛行率，並將其與這個區域甲狀腺腫盛行率作相關。

方法：一個橫斷性研究，從 Semiron 的 108 所城市及鄉村的小學(年齡為 7-13 歲)以多階段隨機集束抽樣選取 1948 名學生。取得父母所簽署的同意書之後，由內分泌醫師評估孩童的甲狀腺腫等級。比較第二級甲狀腺腫孩童(108 名案例)及非甲狀腺腫孩童(111 名孩童為控制組)的抗甲狀腺腫抗體。

結果：整體來說，1948 名學生有 36.7%有甲狀腺腫。平均的尿碘量為 1.49±0.7 μmol/L。這個值在正常的範圍之內。219 名進一步評估的孩童中，4.3%呈現亞臨床低甲狀腺血症，7.3%的抗甲狀腺抗體為陽性。甲狀腺腫與非甲狀腺腫孩童在甲狀腺過氧化酶抗體(anti-TPO)沒有顯著差異(Odds Ratio= 3.2, p= 0.13)，而抗 Tg 則有顯著差異(Odds Ratio: 5.6, 95% CI: 1.18-26.0, p: 0.015)。

結論：本研究指出在這個碘缺乏的區域進行碘的補充之後，自體免疫可能是甲狀腺腫仍然持續存在的機制之一，但是其他因子的角色也應該被考慮。

關鍵字：甲狀腺腫、抗甲狀腺抗體、甲狀腺素過氧化酶抗體、甲狀腺球蛋白抗體、自體免疫甲狀腺疾病。