Persistence of goitre in children post-salt iodization in Islamic Republic of Iran: autoimmune status

M.H. Dabbaghmanesh,1 A. Sadegholvaad,1 F. Ejtehadi1 and G.R. Omrani1

1Department of Internal Medicine, Endocrine and Metabolism Research Centre, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran (Correspondence to M.H. Dabbaghmanesh: dabbaghm@sums.ac.ir).

Received: 10/07/06; accepted: 27/11/06

ABSTRACT We evaluated the prevalence of autoimmune thyroiditis in a random sample of 1188 schoolchildren aged 8–13 years with normalized iodine intake in the Islamic Republic of Iran. The prevalence of goitre was 39.6%; the majority had palpable but non-visible goitre. Of a subsample of 500 children, median urinary iodine excretion (18.8 µg/dL) indicated normal iodine intake. Thyroid peroxidase (TPO) antibody was positive in 3.7% of children and was significantly correlated with the prevalence of goitre and hypothyroidism. No correlation was seen between urinary iodine excretion and positive TPO antibody, mean TPO antibody, hypothyroidism or prevalence of goitre. Autoimmune thyroiditis explains some cases of goitre but other goitrogenic factors need to be evaluated.

Persistance du goitre chez les enfants après iodation du sel en République islamique d’Iran : état auto-immun

RÉSUMÉ Nous avons évalué la prévalence de la thyroïdite auto-immune dans un échantillon aléatoire de 1 188 élèves âgés de 8 à 13 ans recevant un apport d’iode standard en République islamique d’Iran. La prévalence du goitre était de 39.6 % ; dans la majorité des cas, ce goitre était palpable mais non visible. Dans un sous-échantillon de 500 enfants, la valeur moyenne d’excrétion urinaire d’iode (18.8 µg/dL) indiquait un apport d’iode normal. Les anticorps anti-thyroperoxydase (TPO) étaient positifs chez 3.7 % des enfants et significativement corrélés avec la prévalence du goitre et de l’hypothyroïdie. Aucune corrélation n’a été observée entre l’excrétion urinaire d’iode et les anticorps anti-TPO positifs, les taux moyens d’anticorps anti-TPO, l’hypothyroïdie ou la prévalence du goitre. La thyroïdite auto-immune explique certains cas de goitre mais d’autres facteurs goitrogènes doivent être évalués.
Introduction

Iodine deficiency has a number of important health consequences which together are called iodine deficiency disorder. The most serious of these are endemic goitre, hypothyroidism, stillbirth, congenital abnormalities and impairment of intellectual development [1].

Previous national surveys of iodine deficiency in the Islamic Republic of Iran revealed endemic goitre and iodine deficiency in all provinces [2]. The main strategy for control of iodine deficiency was country-wide salt iodization and mandatory production of iodized salt for household use, which started in 1994. Subsequently, the Islamic Republic of Iran became iodine sufficient and this achievement was recognized by the World Health Organization (WHO) Regional Office for the Eastern Mediterranean (EMRO) in the year 2000 [3].

Despite this success, goitre is still endemic in schoolchildren [4]. Now that iodine intake is normalized, causes other than iodine deficiency have to be considered in schoolchildren with thyroid enlargement. The most important differential diagnosis for persistence of goitre is thyroid autoimmunity.

A study in which iodide was administered to patients with goitre showed evidence of autoimmunity [5], with 42.8% developing positive thyroid autoantibodies. Another study showed that increased iodine intake was associated with an increased incidence of autoimmune thyroiditis [6]. However, no study has evaluated the contribution of autoimmunity to the prevalence of goitre in Iranian schoolchildren after the salt iodization programme. We therefore aimed to assess thyroid function and the prevalence of positive thyroid autoantibodies in Iranian schoolchildren 10 years after iodine supplementation was started.

Methods

The study was conducted in Marvdasht, an urban community of approximately 150,000 inhabitants, situated 50 km from Shiraz, the capital of Fars province, from April to November 2005.

The sample was selected from all children aged 8–13 years attending the 97 schools in the area. The sampling frame consisted of the list of schools. We selected 40 clusters from this list by cluster random sampling and 100 schoolchildren in each of the 6 year groups were chosen randomly from the clusters. The selected children (600 boys, 600 girls) and their parents were invited to participate in the study; all except 12 accepted. These 1188 children (598 boys, 590 girls) were enrolled after their parents provided written informed consent. None of them was taking thyroid medication.

For each child, the size of the thyroid was determined by an endocrinologist and graded as non-palpable goitre (grade 0), palpable but non-visible goitre (grade 1) or palpable and visible goitre (grade 2), according to the joint criteria of WHO, United Nations Children’s Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) [7].

Simple random sampling was used to recruit a subsample of 500 (252 boys and 248 girls) from the 1188 children to measure levels of urinary iodine excretion (UIE) and serum level of free thyroxine (T4), free triiodothyronine (T3), thyroid-stimulating hormone (TSH) and thyroid peroxidase (TPO) antibodies. All the children accepted. Blood samples were obtained in the early morning and the serum was separated within 1 hour of sampling by centrifugation.

For measurement of UIE levels, urine samples were obtained in the morning and were frozen until analysis by the digestion method. According to WHO/ICCIDD
recommendations, the median UIE for a population should be 10 μg/dL. Mild iodine deficiency is UIE 5.0–9.9 μg/dL, moderate deficiency 2.0–4.9 μg/dL and severe deficiency < 2.0 μg/dL [7]. Not more than 20% of samples from a population should have UIE < 5.0 μg/dL [8].

Free T4 and T3 measurements were carried out on serum by radioimmunoassay (RIA-gnost T3 and T4, CIS Bio International, France) and TSH was assayed by an immunoradiometric technique (Biosource Europe, Belgium). The normal ranges for free T4, free T3 and TSH were defined as 7–18 pg/mL, 2.00–4.25 pg/mL and 0.3–3.9 IU/mL respectively. Radioimmunoassay was also used for detection of TPO antibodies (TPO antibody kit, Radim, Italy); titres ≥ 50 μg/dL were considered positive.

For statistical analysis, we used SPSS, version 11.5. Data which were normally distributed were expressed as mean and standard deviation (SD) and were compared by t-test. Parameters not normally distributed were expressed as median and were compared by Mann–Whitney and Kruskal–Wallis tests. Comparisons between frequencies were made by the chi-squared test. Statistical significance was set at $P < 0.05$.

Results

Prevalence of goitre

Thyroid enlargement of grade 1 was seen in 37.0% and grade 2 in 2.6% of the whole group of students. Among girls 40.1% had goitre (37.6% grade 1, 2.5% grade 2), whereas in boys 39.0% had goitre (36.3% grade 1,
2.7% grade 2). No significant difference was observed in goitre prevalence between the age groups and sexes (Figure 1).

**UIE**
The median UIE of the subsample was 18.8 μg/dL, with no significant difference between boys and girls (17 μg/dL versus 22.4 μg/dL respectively); 12.2% of children had UIE < 5 μg/dL. UIE was not related to age or sex. The median UIE in students who had goitre was 20 μg/dL and in those without goitre was 18 μg/dL, but the difference was not statistically significant (Figure 2).

**TSH, T₄, T₃**
The mean TSH concentration of the subsample was 2.5 (SD 3.1) IU/mL and mean T₄ and T₃ concentrations were 13.1 (SD 2.9) pg/mL and 3.8 pg/mL (SD 1.0) respectively, without age- or sex-related differences. In 2.5% of the children, TSH values were > 3.9 IU/mL. A concentration > 10 IU/mL was found in only 0.8% of the children. The prevalence of hyperthyroidism was 0.2%.

**TPO antibodies**
Positive TPO antibodies were found in 3.7% of the schoolchildren (7.6% in girls versus 0.5% in boys). The mean TPO antibody titres were 26.9 (SD 191) IU/mL and 46 (SD 257) IU/mL in boys and girls respectively ($P < 0.001$).

Of the children with goitre, 5.1% had positive TPO antibody, with mean 38.9 (SD 2.3) IU/mL, whereas in children without goitre, the prevalence of positive TPO antibody was 2.7%, with mean 18.8 (SD 183) IU/mL ($P < 0.001$).

Positive TPO antibody was found in 6.7% of schoolchildren with hypothyroidism.

---

**Figure 2** Distribution of urinary iodine excretion (UIE) level in male and female schoolchildren in Marvdasht ($n = 500$)
ism but in euthyroid children the positive rate was 3.4% \((P < 0.001)\). There was no significant difference between the presence of thyroid dysfunction and TPO antibody status with level of UIE.

**Discussion**

There has been remarkable global success in the control of iodine deficiency disorders via iodization of salt [9,10]. Although several national surveys in the Islamic Republic of Iran showed a significant reduction in the prevalence of goitre, it is still endemic, even though the country is no longer considered iodine deficient. Despite this progress, our findings indicate persistence of endemic goitre in 39.6% of schoolchildren more than 10 years after salt iodization began. The same problem has been reported by others, suggesting that there may be goitrogenic factors other than iodine deficiency [11–14]. The most common cause of goitre in juvenile populations with normal iodine intake is autoimmune thyroiditis [15]. Genetic factors [16] as well as environmental factors have been shown to induce thyroid autoimmunity [17–19]. Excess iodine induces thyroiditis in genetically susceptible animals [20,21]. The mechanism may be that excess dietary iodine triggers thyroid autoimmunity by increasing the immunogenicity of thyroglobulin [22] or by production of free radicals [20,23]. After the introduction of iodine, an increase in lymphocytic infiltration in thyroidectomy specimens and in prevalence of positive antithyroid antibodies have been seen [5,6,24].

However, iodization has not always resulted in the development of autoimmune thyroid disease [25,26]. In Indian girls there was no definite correlation between UIE level and thyroid autoimmunity [27]. Administration of iodized salt to children in Morocco did not result in any thyroid autoimmune [28]. We did not find a relationship with the presence or absence of thyroid dysfunction or with thyroid autoantibody status and UIE. It seems that the response of the immune system to iodine intake is heterogeneous, depending on the immunogenic background of individuals. In this study, the prevalence of positive anti-TPO antibody, hypothyroidism and hyperthyroidism were compatible with data reported from an iodine-sufficient area [29].

We should mention that there may be inter- and intra-observer variation with the palpation method, especially in the assessment of smaller sizes of goitre. Determination of thyroid size by ultrasonography is the preferred method but we used palpation because ultrasonography of these numbers of schoolchildren is cumbersome and because, in the absence of ultrasonography, the palpation method is regarded as a simple and acceptable alternative.

To sum up, autoimmunity of the thyroid might explain to some extent the prevalence of goitre in the post-iodization phase in this area of the Islamic Republic of Iran, but it is necessary to consider other goitrogens. High thiocyanate exposure can account for a proportion of residual goitre after salt iodization programmes in some areas [30]; deficiency of iron and iodine are major overlapping health concerns in developing countries, and iron deficiency impairs thyroid metabolism and may limit the effectiveness of iodine intervention programmes [31]; vitamin A may modify thyroid hormone metabolism [32]; and selenium is an integral component of enzyme glutathione peroxidase and is a known contributor to endemic goitre [33]. We suggest further investigations into the role of these factors in the persistence of goitre in this area.
References


