High Prevalence of Autoimmune Thyroiditis in Schoolchildren After Elimination of Iodine Deficiency in Northwestern Greece

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The current iodine status and the impact of silent iodine prophylaxis on the prevalence of autoimmune thyroiditis among schoolchildren in a formerly iodine-deficient community in northwestern Greece, were investigated. The findings were compared to those obtained from a similar survey conducted 7 years previously in the same area. A total of 302 schoolchildren (12–18 years of age) from a mountainous area of northwestern Greece were examined for the presence of goiter, and blood and urine samples were collected for assessment of thyroid function, antithyroid antibodies and urinary iodine excretion. In those children (n = 42) with palpable goiter or positive antibodies and/or a thyrotropin (TSH) level greater than 5 mU/L, thyroid ultrasonography was performed to estimate thyroid gland size and morphology. Median urinary iodine concentration in the children was 20.21 µg/dL, indicating sufficient iodine intake. Thyroid function was normal in all but 7 children, who had subclinical hypothyroidism (2.5%). Antithyroid antibodies (antithyroid peroxidase [TPO] and/or antithyroglobulin [Tg]) were positive in 32 children, including those with subclinical hypothyroidism (10.6%). Twenty-nine of these children (9.6%) also had the characteristic echo pattern of thyroiditis on ultrasound and were diagnosed to have autoimmune thyroiditis. In comparison to data from our previous survey 7 years ago, there has been a threefold increase in the prevalence of autoimmune thyroiditis among schoolchildren. In conclusion, silent iodine prophylaxis has resulted in the elimination of iodine deficiency in Greece, and this has been accompanied by an increase in the prevalence of autoimmune thyroiditis.

Introduction

It has been suggested that in areas of iodine deficiency the transition to sufficient or excess iodine intake may precipitate the emergence of thyroid autoimmunity (1,2).

Nutritional iodine deficiency had in the past been an endemic problem in Greece, especially in the mountainous region of northwestern Greece, a southern extension of the Central European Alps. Epidemiologic studies more than 30 years ago demonstrated that the prevalence of goiter, because of low iodine intake, was as high as 60% among schoolchildren in this area (3). Although Greece is one of the countries in which an iodine prophylaxis program has never been officially implemented, nutritional iodine intake has improved in recent years, largely because of commercial availability of iodized salt and improved socioeconomic and nutritional conditions (4).

In our previous studies 7 years ago we found that goiter was still prevalent among schoolchildren in northwestern Greece in the presence of borderline iodine deficiency and that autoimmune thyroiditis was also emerging as a frequent cause of goiter among those children with sufficient iodine intake (5,6).

The aim of the present study was to assess the current iodine status and the prevalence of thyroid autoimmunity among schoolchildren in a formerly iodine-deficient community of northwestern Greece and to compare the findings with those from our previous studies.

Materials and Methods

Subjects

A cohort of 302 schoolchildren (165 girls and 137 boys) 12–18 years of age (mean age, 15.4 ± 1.8 years) were investigated. The children were inhabitants of the small town of Konitsa and the surrounding villages, a mountainous rural community in northwestern Greece with a past history of en-
demic goiter. The survey took place in the high schools of Konitsa. The children, parents, and school authorities were informed of the purpose of the study and gave their consent. All children were examined clinically for the presence of goiter according to World Health Organization (WHO) recommendations (7). A spot urine sample was obtained for measurement of urinary iodine and a blood sample was taken for assessment of thyroid function and detection of antithyroid antibodies. Those children with palpable goiter and/or positive antithyroid antibodies or abnormal thyroid function tests were reexamined at the regional University Hospital of Ioannina, where thyroid ultrasonography was performed to assess thyroid gland size and morphology and thyroid function tests were repeated.

Methods

Thyroid function and autoantibody tests

Serum thyrotropin (TSH), thyroxine (T₄), and triiodothyronine (T₃) concentrations were determined by a microparticle enzyme immunoassay using the AXSYM system (Abbott, Abbott Park, IL). The reference range for serum TSH was 0.3–4.8 mU/L. The within and between assay coefficients of variation (CVs) for these measurements were 3% and 4% for TSH, 3.6% and 4.3% for T₄, and 2.5% and 5.5% for T₃, respectively. Antibodies to thyroid peroxidase (anti-TPO) and to thyroglobulin (anti-Tg) were measured using an enzyme chemiluminescent immunometric assay (DPC Immulite, Los Angeles, CA). According to this method, values for anti-TPO higher than 35 IU/mL and for anti-TG higher than 45 IU/mL were positive. The detection limits for these antibodies were 10 IU/mL and 20 IU/mL, respectively.

Urinary iodine excretion

Urinary iodine concentration was determined in duplicate using the colorimetric ceric ion arsenious acid ash method based on the Sandell-Kolthoff reaction (8,9). The detection limit was 0.2 μg/dL and the recovery rate was more than 95%. The within and between assay CVs were 2.5% and 3.5%, respectively.

Thyroid ultrasonography

Thyroid ultrasonography was performed by real time sonography with an Acuson 128 XP 110, using a 7.0-MHz linear array transducer. The volume for each lobe of the thyroid was calculated using the formula V (mL): 0.479 × d × w × l [where d = depth, w = width and l = length of each lobe in cm] (10). The thyroid volume was the sum of the volumes of both lobes. In addition, the echographic pattern of the thyroid parenchyma was recorded and, in particular, the presence of diffusely or irregularly reduced echogenicity, characteristic of autoimmune thyroiditis (11). Comparisons of the volume of the thyroid gland in boys and girls expressed as a function of age and body surface area were made with the recently revised normative data for thyroid volume in iodine-replete European schoolchildren (12).

Diagnostic criteria for autoimmune thyroiditis

Autoimmune thyroiditis was diagnosed if serum anti-TPO and/or anti-Tg were positive and the echographic pattern of the thyroid gland on ultrasound had the characteristic diffuse or irregular hypoechochogenicity of thyroiditis (11). Subclinical hypothyroidism was diagnosed if serum TSH was above 5 mU/L in the face of normal T₄ and T₃ levels.

Data analysis

Data are presented as means ± standard deviation (SD) or medians as indicated. Nonparametric statistics were used to analyze urinary iodine excretion (Kruskal-Wallis test). Comparisons of urinary iodine content between groups of children were performed using the Mann-Whitney test. Differences in the frequencies of autoimmune thyroiditis and prevalence of goiter among schoolchildren in the present study and those in our previous study (6) were compared by χ² test. Correlations of the various parameters were made by Spearman rank correlation analysis.

Results

Status of iodine nutrition

The median urinary iodine concentration of the examined schoolchildren was 20.21 μg/dL (Q1 16.51 μg/dL, Q3 25.79 μg/dL). According to WHO and International Council for the Control of Iodine Deficiency (ICCIDD) criteria, this indicates sufficient nutritional iodine intake in the area (7). All the children had urinary iodine levels above 12 μg/dL (Fig. 1).

Thyroid function and antithyroid antibodies

Thyroid function was normal in all but 7 children (4 boys, 3 girls) in whom TSH levels were above 5 mU/L in the face of normal T₃ and T₄ levels consistent with subclinical hypothyroidism (2.5%). Positive antithyroid antibodies (anti-TPO and/or anti-Tg) were detected in 32 children (22 girls, 10 boys) including those with subclinical hypothyroidism (10.6%). Anti-TPO antibodies were positive in 25 children (16 girls, 9 boys) and anti-Tg antibodies were positive in 17 children (15 girls, 2 boys). Both antithyroid antibodies were positive in 10 children (9 girls, 1 boy, Table 1).

Further analysis showed no statistically significant difference in median urinary iodine concentration between the children with positive and those with negative antithyroid antibodies (p > 0.05).

Prevalence and cause of goiter

Among the 302 children who underwent clinical examination, 22 (17 girls, 5 boys) had clinically detectable goiter at stage 1 or 2 by WHO/ICCIDD criteria (7). The goiter in 12 of these children was subsequently found on ultrasound to have the characteristic features of thyroiditis. Three children had a small nodular goiter with normal thyroid function and negative antibodies (simple goiter). In the remaining children, the thyroid gland was normal on ultrasound (false-positive). Thus, the overall prevalence of goiter among schoolchildren was 5% and in the majority (80%) the cause was autoimmune thyroiditis.

Thyroid ultrasonography

In total, 42 children underwent thyroid echographic examination. These were children with clinically palpable goi-
ter and/or positive antithyroid antibodies and TSH levels above 5 mU/L. Twenty-nine of these children (20 girls, 9 boys), including the 12 goitrous children, had the echographic pattern of diffuse or irregular hypoechochogenicity and coarseness of the thyroid parenchyma, characteristic of autoimmune thyroiditis. The remaining children had either a simple goiter (n = 3) or normal thyroid glands.

The mean thyroid volume of the children examined by ultrasound was 9.6 ± 4.8 mL. In comparison with the revised normative data for iodine-replete European schoolchildren (12), the thyroid volume of our children expressed as a function of age or body surface area was borderline high (results non shown). This is to be expected for children who had been previously exposed to iodine deficiency.

Prevalence of autoimmune thyroiditis

Twenty-nine children (20 girls, 9 boys) fulfilled the criteria set for the diagnosis of autoimmune thyroiditis (9.6%). Three children with low titer antithyroid antibodies but normal thyroids on ultrasound and normal thyroid function were not included in the diagnosis of thyroiditis.

Comparative data between 1994 and 2001

In Table 2, data on urinary iodine concentration (median values), the prevalence of autoimmune thyroiditis, and the prevalence of goiter among schoolchildren in northwestern Greece in the years 1994 and 2001 (present study) are presented for comparison.

Discussion

In the present study we evaluated the status of iodine nutrition and the prevalence of autoimmune thyroiditis among schoolchildren in a formerly iodine-deficient community of northwestern Greece (5,6). The decision to study the schoolchildren in this particular community was based on the following considerations.

First, this area is one of the core regions in northwestern Greece with a past history of endemic goiter and therefore suitable to study the changes that may have occurred in iodine status. Second, children in this age group are known to be susceptible to changes in iodine intake and therefore reflect better the evolution of respective changes in thyroid

<table>
<thead>
<tr>
<th>Gender</th>
<th>No.</th>
<th>Age mean ± SD</th>
<th>TSH &gt; 5 mU/L</th>
<th>Anti-TPO positive</th>
<th>Anti-Tg positive</th>
<th>Both antibodies</th>
<th>Median UIE (µg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>137</td>
<td>15.3 ± 1.8</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>20.86</td>
</tr>
<tr>
<td>Girls</td>
<td>165</td>
<td>15.5 ± 1.8</td>
<td>3</td>
<td>16</td>
<td>15</td>
<td>9</td>
<td>19.43</td>
</tr>
<tr>
<td>Total</td>
<td>302</td>
<td>15.4 ± 1.8</td>
<td>7</td>
<td>25</td>
<td>17</td>
<td>10</td>
<td>20.21</td>
</tr>
</tbody>
</table>

TSH, thyrotropin; TPO, thyroid peroxidase; Tg, thyroglobulin; UIE, urinary iodine excretion.
biology, and third, this community was included in our earlier survey 7 years ago on the prevalence of goiter in northwestern Greece (5).

Three main points have emerged from this survey. First, the status of iodine nutrition has markedly improved in northwestern Greece as compared with the situation 7 years ago, and is currently adequate. This is illustrated by the fact that median urinary iodine excretion that was borderline low (at 8.4 μg/dL) in 1994, increased to 20.2 μg/dL in the year 2001. During this period no official measures were taken to implement a program of iodine prophylaxis and iodized salt has been commercially available and has replaced noniodine salt in food stores and supermarkets. On the other hand, the public has become aware of the necessity for iodine supplementation. These factors and the use of iodophores in the poultry industry as sanitizing agents, along with improvement in socioeconomic conditions in general have contributed to the process of silent iodine prophylaxis resulting in the improved iodine nutrition of Greek schoolchildren.

Second, the prevalence of goiter has demonstrated a dramatic decrease as a result of this improvement of iodine nutrition and is currently 5.0% in school-aged children. Some 30 years ago the prevalence of goiter in this age group was approximately 60% and 7 years ago had declined to 21% in the same area (3,5). The predominant cause of goiter in the past was iodine deficiency, the predominant cause today is thyroid autoimmunity (13,14).

Third and most important, is the rising prevalence of autoimmune thyroiditis that followed the improvement in dietary iodine intake over the recent years. In our previous study in 1994, the overall prevalence of autoimmune thyroiditis among schoolchildren was 3.3% (6). In the present study the prevalence has increased to 9.6% indicating a threefold increase in the last 7 years. These findings support the end of iodine deficiency and its consequences and the emergence of autoimmune thyroiditis among the young inhabitants in northwestern Greece. It must be emphasized, however, that antibody titers were low in most cases and were not associated with thyroid functional alteration, other than from seven cases of subclinical hypothyroidism and these children are being followed up prospectively.

The increasing incidence of autoimmune thyroiditis is probably the consequence of the increase in dietary iodine intake over recent years in this formerly iodine-deficient area of Greece. Previous clinical and experimental studies have suggested a link between the level of iodine intake and the development of autoimmune thyroid disease (15,16). Thus, the frequency of thyroid autoimmunity in population studies has been shown to increase after iodine prophylaxis and is higher in areas with high iodine intake than in areas with iodine deficiency (17,18). Iodine supplementation in iodine-deficient areas increased the prevalence of lymphocytic infiltration of the thyroid (2,19) and the development of antithyroid antibodies (20). The association has been confirmed in experimental animals by feeding iodine to genetically susceptible animal strains and testing them for thyroiditis and thyroid antibodies (21,22).

The mechanisms by which dietary iodine modulates thyroid autoimmunity are not known, but the following hypotheses have been put forward (22). The first is the iodine toxicity hypothesis, suggesting that iodine in excess can be toxic to iodine-deficient thyroid cells, after being oxidized by endogenous peroxidases and may induce apoptosis of the cells through generation of free radicals (23,24). The second hypothesis is the increased immunogenicity of highly iodinated Tg, based on observations that enhanced iodination of Tg facilitates the selective presentation of a cryptic pathogenic peptide in vivo or in vitro (25,26). Others have suggested a direct stimulating effect of iodine and iodinated compounds on cells of the immune system (22,27). Clearly, more studies are required to clarify the role of excess iodine in triggering and/or causing thyroid autoimmunity.

Another point of discussion is that in our previous study, which took place at a time of borderline iodine deficiency, antithyroid antibodies were more prevalent in children with higher urinary iodine content than in those with low urinary iodine (6). In contrast, in the present study in iodine-replete children, such a relationship between urinary iodine excretion and thyroid autoimmunity was not longer evident. These findings may suggest that excess iodine may not be the sole factor in determining the development of thyroid autoimmunity and may only play a permissive role in the background of genetic predisposition (22). Further studies are needed to determine the interaction between genetic factors and iodine intake in the manifestation of thyroid autoimmunity.

Finally, the more frequent occurrence of antithyroid antibodies in girls than in boys is previously well documented and is consistent with the higher prevalence of autoimmune thyroid diseases in women (28).

In conclusion, the findings of the present study indicate that silent iodine prophylaxis in Greece has resulted in elimination of iodine deficiency, but this beneficial effect has come with a price, which is the emergence of autoimmune thyroiditis among schoolchildren.

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References


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