Improvement of iodine deficiency after iodine supplementation in schoolchildren of Azerbaijan was accompanied by hypo and hyperthyrotropinemia and increased title of thyroid autoantibodies


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ABSTRACT. Objective: In the mountainous areas of Azerbaijan the schoolchildren suffer from severe Iodine Deficiency (ID) with median Urinary Iodine excretion (UIE) 36 mcg/l and prevalence of goiter 99% (estimated by US). In a population of 293,000 schoolchildren aged 8-14 y.o. we administered capsules containing 190 mg of iodized oil (Lipiodol-® Guerbet, Cedex, France) twice yearly in 6 months apart (total 380 mg). The aim of the present study was to evaluate the efficacy, the benefits, as well as the possible side-effects in a follow-up period of 6 and 12 months after the initial administration of iodized oil. Methods: Six and 12 months after the initial administration of iodide, two representative samples of 391 and 326 children respectively were examined. The evaluation included: estimation of goiter by US, determination of UIE and serum measurements of T₃, T₄, TSH, Tg, autoantibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg). Results: There was an improvement in median UIE which increased from 36 mcg/l to 68 and 81 mcg/l after 6 and 12 months of treatment respectively. The prevalence of goiter decreased from 99% to 54% and 26% respectively. Tg was decreased at 6 and 12 months from the first administration, whereas TSH remained unchanged at 6 months and decreased at 12 months when compared to the latter value. Hypothyroidism was detected in 7% of children after iodide administration both at 6 and 12 months, but overt hypothyroidism was observed only in 0.5% at 12 months. Subclinical hyperthyroidism was detected in 2% and 6% after iodide administration both at 6 and 12 months. There was a significant increase in the title of thyroid autoantibodies in 6 months which was retained and increased in 12 months. There was no relation between the appearance of thyroid dysfunction and the positive thyroid autoantibodies. Conclusion: The dose of 190 mcg iodide administered twice yearly, improved iodine deficiency and endemic goiter in schoolchildren. The increase of UIE resulted from iodide administration, was accompanied by an increased title of thyroid autoantibodies and an increased prevalence of hyper- and hypothyrotropinemia apparently of no autoimmune etiology. (J. Endocrinol. Invest. 26: 43-48, 2003)

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INTRODUCTION

Despite the "war" against Iodine Deficiency (ID) and related disorders (Iodine Deficiency Disorders-IDD) it has been estimated that according to WHO/UNICEF/ICCIDD (International Council for the Control of Iodine Deficiency Disorders) 130
out of 191 countries still suffer from ID (1). We have previously reported that Azerbaijan presents moderate to mild ID with high prevalence of goiter (2). In this study we have found that schoolchildren living in the mountainous regions, particularly in the area of Caucasus are suffering from severe to moderate ID according to WHO/UNICEF/IJCCIDD criteria (3). The median Urinary iodine excretion (UIE) was 36 mcg/l and goiter prevalence was 99% by US and 87% by palpation. We concluded that in these mountainous and isolated regions, an urgent intervention for prompt prevention from ID consequences was needed (2).

The aim of the present study was to evaluate the efficacy, the benefits, as well as the possible side-effects in a follow-up period of 6 and 12 months after the initial administration of iodized oil.

SUBJECTS AND METHODS

The study was conducted under the auspices of the Greek non-governmental humanitarian organization "Doctors of the WorldGreece" and with the authorization of the Government and Ministry of Health of Azerbaijan.

In children aged 8-14 year old (no. <293,000) living in the mountainous regions of Caucasus, capsules containing 190 mg of iodized oil (Lipiodol® Guerbet, Cedex, France) were administered twice yearly once every 6 months (total 380 mg). Six and 12 months after the initial administration of iodide, two samples of 391 (197 males, 194 females) and 326 (166 males, 160 females) children were used for evaluation. These subjects were selected randomly from 7 different representative areas with severe iodine deficiency (Oguz, Qax, Sheki, Balaken, Ismayilli, Quabala, Zakatala) out of 13 studied areas of the country of Azerbaijan (2). In four (4) out of the 7 areas (Oguz, Qax, Sheki, Balaken) the samples were obtained exclusively from children attending the same school, in each area. The studied areas and the number of studied schoolchildren are shown in Table 1. The initial evaluation protocol was applied at the follow-up and included the following: 1. Registration of personal data (name, sex, age), height and weight measurements. 2. Ultrasound assessment of thyroid volume by portable ultrasound apparatus with a 7.5 MHz linear transducer (Scanner 100 LC Pie Medical, Phillips Medical Systems Company, Maastricht, Netherlands). The volume of each lobe was calculated according to the formula for a volume of a rotation ellipsoid by multiplication of maximal thickness, width and height of the lobe by the correction factor 0.479 (4,5). The upper limits of normal values were estimated according to Body Surface Area (BSA), as proposed by Delange et al. (6). 3. Indine determination in urine was performed by the spectrophotometric method (Sandell-Kolhoff reaction, after digestion with chloric acid at 110°C for 1 hour) according to the method of Dunn et al. (7). The samples were refrigerated at -4°C and assayed at the Endocrine Laboratory of the University of Patras Medical School, Greece. Serum determinations of T3, T4, TSH, TG, auto antibodies against thyroid peroxidase (anti-TPO) and Tg (anti-Tg) were performed in samples, refrigerated at -4°C, transported and assayed at the Endocrine Laboratory of Patras Medical School, Greece. T3, T4 and TSH determinations were analyzed by a semi-automatic analyzer IMX (Abbott Park, Illinois, USA). For the measurement of anti-TPO a radioimmunossay kit (B.R.A.H.M.S., Dyno test, Diagnostica GmbH, Berlin, Germany) was used. For the measurement of anti-Tg an immunoradiometric assay (IRMA, CIS bio international, Yvette, Cedex, France) was used. Serum Tg was determined by IRMA (DiaSorin, Saluggia,Italy).

Normal range: T3: 0.8-2.0 ng/ml, T4: 4.5-12.5 μg/dl, TSH: 0.2-2.5 mU/l. As increased TSH suggesting hypothyroidism we used values above the 4.2 mU/l. Tg: <46 ng/ml, antiTPO: <60 u/ml, antiTG: <50 u/ml.

Statistics: Significance of differences between median values was evaluated using non-parametric statistical tests. Specifically, the Mann-Whitney test was used for two groups and the Kruskal-Wallis test for more than two groups. Comparisons among categories were made with the use of chi-squared test, taking into account the appropriate corrections when applicable (continuity corrections etc.). Log linear analysis was employed for the investigation of dependence among the follow-up period, thyroid dysfunction and thyroid auto antibodies.

RESULTS

There was a significant improvement in median UIE which increased from 36 mcg/l prior to administration, to 68 and 81 mcg/l after 6 and 12 months respectively.

The prevalence of goiter as estimated by US decreased after 6 and 12 months of treatment, from 99% to 54% and 26% respectively. Median serum T3, T4, TSH, Tg values and thyroid volume prior and 6 and 12 months after treatment in the 4 areas where samples were obtained exclusively from children attending the same school, in each area (Oguz, Qax, Zakatala, Balaken) are presented in Table 2. Serum Tg was decreased at 6 and 12 months after the initiation of iodide treatment.

Table 1. The studied areas and the number of studied schoolchildren

<table>
<thead>
<tr>
<th>Iodide administration</th>
<th>Before</th>
<th>6 months after</th>
<th>12 months after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oguz</td>
<td>53</td>
<td>71</td>
<td>52</td>
</tr>
<tr>
<td>Qax</td>
<td>50</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>Sheki</td>
<td>52</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Balaken</td>
<td>59</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>Ismayilli</td>
<td>–</td>
<td>64</td>
<td>56</td>
</tr>
<tr>
<td>Quabala</td>
<td>–</td>
<td>64</td>
<td>45</td>
</tr>
<tr>
<td>Zakatala</td>
<td>52</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>266</td>
<td>391</td>
<td>326</td>
</tr>
</tbody>
</table>

44
Porarary measure (8). Orally administered iodized oil is the preferred mode of administration as the im route is difficult to implement, is more expensive, may carry risks of transmissible diseases and transient, painful induration at the injection site has been reported (8). We therefore administered twice 190 mg of iodide orally within an interval of 6 months in 293,000 schoolchildren. This resulted in a drastic increase in UIE from 36 mcg/l to 81 mcg/l, 12 months following the initial iodide administration. This increase in the values of median UIE indicates a shifting from severe to mild iodine deficiency approaching the value of 100 mcg/l which is considered normal (3).

The doses usually used in children varies in different studies from 118 to 240 mg of iodide in a single dose for 6 or 12 months (9-11). The observed increase of UIE in our study is in concordance with the results of these studies, although substantially higher values were reported in the reports quoted above.

The prevalence of goiter was markedly decreased in 6 and in 12 months after the first administration. This reduction in goiter is comparable to that observed in other studies (9, 11). It is well known that the estimation of goiter prevalence is more precise and reliable by US than by palpation (12). However, the upper limits of normal by US varies in different countries (13). Recent data indicate that there are significant interobserver and intraobserver variations in sonographic measurement of thyroid volume in children (14) and these variations contribute to these differences (15). For these reasons the correction of estimated thyroid size by US by the BSA, which we applied in this study, should be preferred especially in developing countries (16).

As expected, serum Tg values were decreased and was appropriate to the observed increase in UIE (3,17). TSH was essentially unchanged although there was a tendency to decrease at 12 months. This is in agreement with the notion that serum Tg and TSH are more sensitive indicators of iodine sufficiency than serum T4 and TSH concentration (3).

The proportion of positive auto-antibodies, either anti-TPO or anti-Tg increased after the first administration of iodide. Clinical studies have shown that the increase of iodine intake in iodine deficient areas is accompanied by increased autoimmunity (18, 19). These data are supported from epidemiological studies (20, 21). The increased proportion of positive thyroid auto-antibodies in our study is not related to increased levels of UIE since we did not observe UIE values greater than 300 mcg/l at least for the 12 months follow-up. The levels of UIE although substantially increased, remained slightly under the lowest limits of normal. However the abrupt increase in iodine intake might be important for the development of autoimmune, although the exact mechanism is not clear. Several mechanisms have been proposed including the increased immunogenicity of the well iodinated Tg, damage to thyroid tissue because of iodide excess, decrease in free radical scavenger capacity and increased antigen presentation and inflammatory processes (22). Studies in the bioavailability of oral vs iodinated oil in healthy subjects have shown that the maximum UIE is achieved on day 1 for the oral route and on day 13 for the im route (23), which means that at least for the early days after iodide administration, the thyroid was exposed to excessive iodine load. The latter may also explain the increased prevalence of thyroid dysfunction and especially subclinical hypothyroidism.

It is noteworthy that the observed hyper TSH as well as hypothyrotoxemia are not associated with positive thyroid auto-antibodies in our study. Iodine-induced hypothyroidism has been observed in a few apparently normal individuals, in newborn and fetuses, in some patients with chronic systemic diseases, in euthyroid patients with autoimmune thyroiditis and in patients with no apparent thyroid diseases (24). In humans, maturation of hypothalamic-pituitary-thyroid axis is a complex process starting from midgestation and ending in adult life (25). Transient elevated TSH levels have been noted af-

### Table 4. Thyroid auto antibodies and thyroid dysfunction 6 and 12 months after the first administration of 190 mg iodized oil.

<table>
<thead>
<tr>
<th></th>
<th>6 months after</th>
<th>TSH mIU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid auto antibodies (a-TPO and/or a-Tg)</td>
<td>&lt;0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Negative</td>
<td>84</td>
<td>257</td>
</tr>
<tr>
<td></td>
<td>TSH mIU/ml</td>
<td>12 months after</td>
</tr>
<tr>
<td>Thyroid auto antibodies (a-TPO and/or a-Tg)</td>
<td>&lt;0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>260</td>
</tr>
</tbody>
</table>

The relationship among TSH, auto antibodies and follow up period was investigated using log-rank analysis. The dependence among the variables of interest was determined with the adoption of the backward elimination model selection technique that starts from the saturated model (all variables considered a priori dependent on each other). The Kruskal-Wallis and Jonckheere-Terpstra were used.
Treatment of iodine deficiency in Azerbaijan

It is clear that excess iodide administration to normal iodine efficient (25, 27) and iodine deficient children (28); it should be emphasized however that the effect of iodide on the release mechanism of T4 and T3 in children is not clearly understood. It is possible that thyroid in children may be more sensitive to the inhibitory effect of iodide on the proteolysis of Tg and therefore the magnitude of transient hyperthyrotropinemia may reflect a compensatory effect of TSH on the inhibitory effect of iodide on the release mechanism accompanied by increased compensatory response of TSH to this mechanism. The incidence of iodine-induced hyperthyroidism increases in iodine deficient countries after the implementation of iodized oil or salt. This is mainly observed in adults who have been for long exposed to iodine deficiency and is associated with thyroid nodularity (29). We have not observed clinically overt hyperthyroidism in our sample. This is probably due to the young age of the individuals, the short time of exposure to ID and to the absence of nodularity (2). It should be pointed out that in iodine deficient adults, as well as in children, the iodide induced thyroid dysfunction and the autoimmunity, are reversible (30). We believe that these small aberrations are transient and normal thyroid function will be restored.

There is no doubt that the use of iodized salt is the treatment of choice to confront ID with safety and sustainability. The use of alternative methods such as iodized oil either orally or by injection is necessary for immediate intervention (31). The acute increase in iodine intake may have some unfavorable transient side effects, but the final effect is far more beneficial (32). In conclusion, the dose of 190 mg iodide given twice yearly, markedly improves the iodine deficiency and endemic goiter in schoolchildren in severely affected areas of Azerbaijan. The increase of UIE, resulted from iodide administration, was accompanied by an increased titre of thyroid autoantibodies and an increased prevalence of hyper- and hypothyrotropinemia apparently of no autoimmune etiology.

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REFERENCES


