Thyroid volume and morphology and urinary iodine excretion in a Danish municipality

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In order to throw light upon the eventual need for iodine supplementation in Denmark, four age groups of women (15, 30, 45 and 60 years) from the Holbaek municipality were invited for a clinical and ultrasound study of thyroid volume, structure and function. Of the 570 women invited, 391 accepted and were divided into the following groups: group I: 15 years, N = 113; group II: 30 years, N = 100; group III: 45 years, N = 98; group IV: 60 years, N = 80. The results were as follows: the thyroid gland was palpable in 39% and visible in 16% of the entire group; 19% had a family history of thyroid disorders and 7.6% had a previous thyroid disorder. Thyroid volumes (median (range)) as measured by ultrasound were 12 ml (4–29 ml), 18 ml (5–47 ml), 18 ml (7–64 ml) and 18 ml (9–51 ml) in groups I–IV, respectively. The calculated 24-h iodine excretion was 65 μg (19–365 μg), 88 μg (15–274 μg), 97 μg (40–737 μg) and 83 μg (50–999 μg) in groups I–IV, respectively. An abnormal echo structure was present in 3, 10, 21 and 30%, respectively. Defining a goitre as a thyroid volume above 28 ml indicated a goitre prevalence of 17% in females aged 30–60 years in the Holbaek area of Denmark. Among the 60-year-old women, 3% had a clinically significant goitre (WHO grade III). Thyroid volume did not correlate with iodine excretion. The benefit of iodine supplementation is discussed.

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Previous studies on daily iodine intake in Denmark unanimously showed a relatively low iodine intake, with median values varying from about 45 to 75 μg (1–4). The WHO recommended daily intake of iodine is 150–200 μg. A higher intake will not reduce further the incidence of goitre (5). Nevertheless, mandatory or voluntary iodine prophylaxis has not been established in this country, although it has been considered. The reason for not giving iodine supplementation was, among others, that the benefit could not be measured because the prevalence of goitre was unknown. Further, it was estimated that a significant although self-limiting increased rate of hyperthyroidism following higher iodine intake might occur (6).

The aim of this study was to measure the distribution of gland size and to estimate the prevalence of goitre in four age groups of women in a single community, based on sonography measurement of thyroid gland volume and structure, and to evaluate whether or not there is a correlation between iodine excretion and goitre.

Material and methods

Study groups

Five hundred and seventy women born in 1975, 1960, 1945 and 1930 were selected by date of birth in a municipality (Holbaek) in Denmark and invited to participate in the investigation. A total of 391 (68.5%) accepted. The age groups represented were: group I: N = 113, 15 years; group II: N = 100, 30 years; group III: N = 98, 45 years; group IV: N = 80, 60 years. Four of the women were pregnant and 13 were lactating, all from group II.

Clinical data

The clinical examination was performed by the same person (B Nygaard) in 1990–1991. A questionnaire included: family history of thyroid disorders; previous thyroid and other illness; drugs, including vitamins and natural remedies; menstrual cycle; and smoking and drinking habits. Body weight and height were measured. Thyroid size was estimated by inspection and palpation and classified as grade 0–III according to WHO: 0A: thyroid gland not palpable; 0B: thyroid gland distinctly palpable, but not visible with the head in normal or raised position; I: thyroid gland easily palpable and visible with the head in raised position; II: visible goitre with head in normal position; III: large goitre (5). The glands were classified as diffuse, multinodular or having a solitary process.
Owing to skewed distribution of data, in most cases both medians and ranges are given. For symmetrically distributed parameters, however, and for comparisons of groups, Student’s t-test and the F-test were applied. For skewed data, logarithmic values were used. The level of significance is defined as p<0.05.

Ultrasonic examination

All subjects were examined by the same person (P Gideon) using a Hitachi Tomosonic EUB-25M real-time scanner with a 5-MHz linear transducer. The subjects were examined with the neck hyperextended. 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, as described by Brunn et al. (7). The average error of this method is 16% (SEM). The echogenicity was described as diffuse, multinodular, solitary adenoma or one or more cysts.

Urinary iodine excretion

Based on 5-h urine samples, the 24-h iodine excretion and the excretion of iodine/g creatinine were calculated. Urinary iodine was measured by a modified method based on arsenic acid reduction of ceri ions (8).

Thyrotrophin and thyroid hormone concentrations

A total of 362 subjects accepted blood sampling for the determination of thyrotrophin (TSH). If the TSH concentration was less than 0.2 mU/l or higher than 3.5 mU/l, the total concentrations of triiodothyronine (T3) and thyroxine (T4) and the T3–resin uptake were measured. Thyrotrophin was measured using a commercial enzyme-immunological method (Amerlite TSH-60 by Amersham International, Amersham, UK). The normal range of TSH concentration is 0.2–3.5 mU/l.

T3, T4 and T3–resin uptake were determined with in-house methods.

Technetium-99m scintigraphy

Subjects having a solitary adenoma diagnosed by ultrasound and/or palpation were offered scintigraphy.

Statistics

The distribution of thyroid volume is given in Fig. 1. The distribution is increasingly skewed with age, indicating a

<table>
<thead>
<tr>
<th>Table 1. Thyroid volume and smoking habits.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Non-smokers (%)</td>
</tr>
<tr>
<td>Median (ml)</td>
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<tr>
<td>Range (ml)</td>
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<tr>
<td>0–10 cigarettes/day (%)</td>
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<tr>
<td>Median (ml)</td>
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<tr>
<td>Range (ml)</td>
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<tr>
<td>&gt;10 cigarettes/day (%)</td>
</tr>
<tr>
<td>Median (ml)</td>
</tr>
<tr>
<td>Range (ml)</td>
</tr>
</tbody>
</table>

Results

Clinical data

Seventy-four (19%) women had a family history of thyroid disorders among parents, grandparents, sisters, brothers and/or children. Thirty (7.6%) women had a goitre or other thyroid disorder diagnosed prior to this study, eight had a subtotal thyroidectomy and four received thyroid hormone treatment for hypothyroidism.

Ninety-three women took iodine supplementation (100–150 μg) and thus had a significantly higher iodine excretion: 117 μg/24 h compared to 78 μg/24 h in the rest of the group.

Smoking habits are listed in Table 1. None consumed more than 100 g of alcohol per day. In the four groups, 0%, 1%, 12% and 11%, respectively, had a daily consumption of alcohol.

Body weight was considerably lower in group I than in the other groups: 56 kg (40–84 kg) and 65 kg (46–104 kg), respectively. The height was significantly lower in group IV than in the other groups: 161 cm (145–174 cm) in group IV as compared to 165 cm (147–182 cm) in groups I–III.

WHO classification of thyroid gland size

The distribution is given in Table 2. Goitre grades II and III were found only in women of 30 years or more. A solitary adenoma was palpated in a total of five women (groups II–IV). Multinodular goitre was diagnosed in 10 women from groups II–IV. Three per cent (two women) of group IV had a clinically significant goitre (grade III).

Ultrasound study

The distribution of thyroid volume is given in Fig. 1. The distribution is increasingly skewed with age, indicating a
Table 2. Thyroid size (%) in 15–60-year-old women.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>OA</th>
<th>OB</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–60 (N = 391)</td>
<td>61</td>
<td>23</td>
<td>10</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>15 (N = 113)</td>
<td>72</td>
<td>19</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 (N = 100)</td>
<td>45</td>
<td>32</td>
<td>15</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>45 (N = 98)</td>
<td>58</td>
<td>28</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>60 (N = 80)</td>
<td>68</td>
<td>18</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

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<th>OB</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
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<td>10</td>
<td>5</td>
<td>1</td>
</tr>
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<td>72</td>
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<td>0</td>
<td>0</td>
</tr>
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<td>45</td>
<td>32</td>
<td>15</td>
<td>8</td>
<td>0</td>
</tr>
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<td>28</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>60 (N = 80)</td>
<td>68</td>
<td>18</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

The value is significantly lower in group I (p < 0.005) but no difference of median values was found between groups II, III and IV. Thyroid volume was correlated positively with body weight, height and body mass index (p < 0.005). The values increased between groups I and II but thereafter there was no significant increase. For the whole group we found, by multiple regression analysis, a formula that describes the relation between thyroid volume, weight and age: thyroid volume (ml) = 2.57 + 0.18 × weight (kg) + 0.11 × age (years). In groups II–IV we found the relation: thyroid volume (ml) = 9.35 + 0.17 × weight (kg).

Structural changes were diagnosed by ultrasound in 15% of the women. The incidences of these changes increased with age from 3% to 30% (Table 3) and
became multifocal. The mean difference between the right and left lobe was 1.27 ml (p < 0.0005), the right lobe being larger.

The gland was significantly larger (p < 0.0005) in smokers than in non-smokers (Table 1).

Thyroid volume in women who had a family history of thyroid disorders was 17.8 ml (8–64 ml) as compared to 16.8 ml (8–54 ml) in those without (p < 0.005). There was no significant influence of menstrual cycle or alcohol habits and no difference between 17 pregnant breast-feeding mothers and the rest of the group.

Comparison between WHO classification of goitre and ultrasound thyroid volume

Table 4 shows a poor relationship between the two methods. Out of 391 women, 43 (11%) had thyroid volumes above 28 ml, of which 60% (26 goitres) were completely overlooked by palpation. On the other hand, small glands were correctly diagnosed clinically in 92% of 288 women and slightly overestimated in 6%.

Technetium-99m scintigraphy

A total of 11 women were offered scintigraphy owing to abnormalities found by palpation and/or ultrasound. Among the nine persons who accepted; four had a normal scintigram; two had multinodular glands and one had an irregular uptake due to previous operation; and two had a 1-cm adenoma shown by ultrasound, which were hypo- and non-functioning scintigraphically but not palpable.

Iodine excretion

The median daily iodine excretion was 83 μg or 75 μg/g creatinine (Table 3, Fig. 2). The excretion was significantly lower in group I (p < 0.005) than in the other groups.

No correlation could be shown between iodine excretion and thyroid volume. Comparing the glandular volumes of those with 24-h urinary iodine excretion below 50 μg to the rest of the group showed no difference.

Thyroid function

The TSH concentration was normal or subnormal in all but three women from group IV. A total of 16 women (4%) had a subnormal TSH concentration, all of whom had normal T₃ and T₄ serum concentrations. One was hypothyroid: the TSH concentration was 21 mU/l and the thyroid hormone concentrations were subnormal; she had no goitre. The four age groups did not differ. There was, however, a significant inverse correlation (p < 0.0005) between thyroid volume and TSH. The TSH concentration was 0.9 mU/l in glands below 20 ml, 0.7 mU/l in glands of 20–30 ml and 0.6 mU/l in glands exceeding 30 ml.

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Table 3. Thyroid volume and morphology and urinary iodine excretion in 391 women.*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Volume (ml)</th>
<th>Abnormal structure (%)</th>
<th>Iodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (N=113)</td>
<td>12 (4-29)</td>
<td>3</td>
<td>65 μg/day (19–365)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>59 μg/g creatinine (25–320)</td>
</tr>
<tr>
<td>30 (N=100)</td>
<td>18 (5-47)</td>
<td>10</td>
<td>88 μg/day (15–274)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 μg/g creatinine (8–560)</td>
</tr>
<tr>
<td>45 (N=98)</td>
<td>18 (7-64)</td>
<td>21</td>
<td>97 μg/day (40–737)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>84 μg/g creatinine (30–399)</td>
</tr>
<tr>
<td>60 (N=80)</td>
<td>18 (9-51)</td>
<td>30</td>
<td>93 μg/day (50–999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>92 μg/g creatinine (34–999)</td>
</tr>
<tr>
<td>15–60 (N=391)</td>
<td>16 (4-64)</td>
<td>15</td>
<td>83 μg/day (15–999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 μg/g creatinine (8–999)</td>
</tr>
</tbody>
</table>

* Values are medians with ranges in parentheses.

Table 4. Relation between clinical and sonographic assessment of thyroid gland size in 391 women.

<table>
<thead>
<tr>
<th>Sonography (ml)</th>
<th>WHO grade</th>
</tr>
</thead>
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<tr>
<td></td>
<td>OA, OB</td>
</tr>
<tr>
<td>&lt;20</td>
<td>266</td>
</tr>
<tr>
<td>20–28</td>
<td>43</td>
</tr>
<tr>
<td>&gt;28</td>
<td>26</td>
</tr>
<tr>
<td>Total no.</td>
<td>335</td>
</tr>
</tbody>
</table>

Fig. 2. Iodine excretion in urine in 391 15–60-year-old women. Eight women who had an iodine excretion above 400 μg/24 h are not shown.
Discussion

Ultrasoundography today is considered to be the golden standard for estimation of thyroid gland volume and goitre prevalence—at least in relatively homogeneous and not severely enlarged glands. A very accurate and precise method has been described by Hegedüs et al. (9) who, by adding slices measured with an interval of 0.5 cm, found a sem of 6% for small glands. Brunn’s method (7)—in spite of a lower precision—has been used in this study, as in the majority of previous studies. Special equipment is not needed, and when studying relatively small glands—as in our study—the thyroid lobes can be assumed to be approximate ellipsoids, thereby fulfilling the criteria for using Brunn’s calculation.

The WHO classification of goitres by inspection and palpation (5) is suitable for measuring goitre prevalence in heavily affected areas with a high proportion of large goitres. We found, as in previous studies (10, 11), a poor correlation between the clinical and ultrasonographic volume estimates. Small diffuse goitres cannot be separated from normal glands by palpation; thus, more than half of the glands exceeding 28 ml in our study were classified as grade 0 by palpation.

The daily urinary iodine excretion is accepted as a reliable estimate of iodine intake. It has, however, been shown that a 5-h urine sample is representative of the 24-h excretion and of the iodine/creatinine ratio (3). We chose this method for obvious practical reasons. It has been shown that the iodine content of Danish food is slightly higher during winter than during summer (2). This study was performed during three different periods: March–April 1990, November–December 1990 and February–March 1991. We found slightly, but insignificantly, lower values during the first period as compared to the second. As no group was studied during summer-time, and because of the large interindividual difference in iodine intake—a high proportion of women were taking iodine-containing vitamins—the seasonal variation in iodine content in the food is considered to be insignificant for the results of this study. The median iodine excretion was slightly higher than in previous Danish studies (Table 5).

All of the women in our study came from one community in Denmark, the majority having stayed there all their lives. Are they representative of the Danish population with regard to iodine intake and goitre size? In Copenhagen, Hegedüs et al. (9) studied normal nongoitrous persons aged 18–90 years and found a median thyroid volume of 18 ml (8–33 ml) that was slightly larger in men than in women. In Germany, median thyroid volumes of 13–19 ml were found in areas with similar or slightly lower iodine intake (12, 13, 15), whereas in Sweden (13) and Holland (17) the volumes were 7 and 10 ml, respectively. In these countries the daily iodine excretion was 173 and 147 µg/g creatinine, respectively. The very similar results from various areas of Denmark and the agreement with results from other countries seem to support that our material is representative of this country.

Thyroid volume increased with age from 15 to 30 years only. A similar correlation has been found previously (9, 17), indicating that after puberty the normal gland has a constant volume.

In our study there was no correlation between iodine excretion and thyroid volume. Such a correlation is rarely seen within one single area, although it is evident when different geographical areas are compared (Table 5).

The definition of “normal” thyroid volume is not clear. In this study 17% of women above 30 years had thyroid volumes above 28 ml, which we tentatively defined as the upper normal limit. Hintze et al. (12) defined the normal range in women as being glands of less than 18 ml and accordingly found a high prevalence

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### Table 5. Epidemiological surveys of thyroid volume and morphology by ultrasound and iodine excretion in urine.

<table>
<thead>
<tr>
<th>Ref. no.</th>
<th>Subject</th>
<th>Volume (ml)</th>
<th>Abnormal structure (%)</th>
<th>Iodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>569 women &gt; 60 years Germany</td>
<td>19.2 ± 25.3</td>
<td>48.6</td>
<td>62 µg/g creatinine (6–7135)</td>
</tr>
<tr>
<td>13</td>
<td>303 women Sweden (2.5–34)</td>
<td>6.9</td>
<td>3.6</td>
<td>173 µg/g creatinine ± 224</td>
</tr>
<tr>
<td>14</td>
<td>1397 women Germany (2.6–124)</td>
<td>13.3</td>
<td>16</td>
<td>84 µg/g creatinine ± 94</td>
</tr>
<tr>
<td>15</td>
<td>76 women Finland</td>
<td>6.7 ± 1.4</td>
<td>1.3</td>
<td>15 µg/g creatinine (5–494)</td>
</tr>
<tr>
<td>16</td>
<td>437 women Germany (4.4–130)</td>
<td>15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>6000 men Denmark 17–20 years</td>
<td>17.5 ± 4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>40 women Denmark 20–80 years</td>
<td>64 µg/day ± 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>132 women Denmark</td>
<td>10.7 ± 4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>30 women Norway</td>
<td>76 µg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>18 Finland</td>
<td>165 µg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>19 Finland</td>
<td>300 µg/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Median values ± SD or mean values and ranges in parentheses.
of goitre in females (54%). His study group was older than ours but the results are very similar.

The adjustment of thyroid volume to iodine intake is physiological. The process of hypertrophy may, however, initiate nodular hyperplasia and autonomy. Such abnormal processes—following physiological adjustment to low iodine intake or goitrogens, and probably modified by genetic factors—are known to become more frequent in very low iodine intake areas. It might be proposed that an "optimal" rather than "normal" median thyroid volume should be defined in order to include the concept of minimal risk of developing clinically significant goitre. Such a definition implies that the increase of thyroid gland volume and pathology—as related to iodine intake—forms a continuum. It also implies an increasingly skewed distribution of thyroid gland volume with age in low iodine intake areas. Although longitudinal studies have not been performed, a comparison of our gland volume distribution to that of Hintze et al. (12) may be taken as a confirmation of this assumption. Finally, it has been shown that increasing gland volume and nodularity gradually suppresses the TSH concentration (20), also indicating a continuum of increasing gland size into increasing degrees of nodular goitre with autonomy.

It seems reasonable to assume that the lower the median thyroid volume, the lower the risk of significant goitre. The "optimum" thyroid volume seems close to 10 ml in adults, corresponding to at least 150 µg of iodine intake per day.

Goitrogens other than insufficient iodine intake and tobacco have not been identified in this country. Iodine kinetics have been studied (21), and such studies did not indicate any widespread genetic defect in patients with non-toxic goitre, such as deficient organic iodine binding, as a conditioning factor.

Systematic iodine supplementation has not been introduced in Denmark. This study—together with the present knowledge of goitre development—can be taken as an impetus to do so, in spite of the fact that out of our 391 women few had significant thyroid disorders: five had hypothyroidism, two had grade III goitre, eight had previous thyroid surgery, two had previous thyrotoxicosis and three had thyroiditis, a total of 20 women or 5%, of which the majority (15/20) might be related to iodine deficiency.

Taking into account older age groups with a higher frequency of thyroid disorders, we estimate that at least 5% of women in Denmark need treatment for iodine deficiency-related disorders of the thyroid gland.

References
19. Lamberg B. Endemic goitre in Finland and changes during 30 years of iodine prophylaxis. Endocrinol Exp 1986;20:35–45

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