The Prevalence of Undiagnosed Thyroid Disorders in a Previously Iodine-Deficient Area

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Objective: The aim of the present study was to analyze the current status of morphologic and functional thyroid abnormalities in a previously iodine-deficient area. Methods: The population based Study of Health in Pomerania (SHIP) comprised 4310 participants, aged 20–79 years. Thyroid function (thyrotropin [TSH] free triiodothyronine [FT₃], and free thyroxine [FT₄]) and serum autoantibodies to thyroperoxidase (TPOAb) were evaluated from blood samples. Thyroid structure and size were measured by ultrasound. Data from 3941 participants with no known thyroid disorders were analyzed. Results: The median iodine urine excretion was 12.4 μg/dL. The rate of decreased serum TSH levels (<0.3 mIU/L) was 11.3%; 2.2% of participants had suppressed serum TSH levels (<0.1 mIU/L). The prevalence of subclinical hyperthyroidism was 1.8%, the prevalence of overt hyperthyroidism 0.4%. Elevated TSH levels were found in 1.2% of individuals. Subclinical hypothyroidism was observed in 0.5%, overt hypothyroidism in 0.7% of the sample. Elevated TPOAb were detected in 7% of subjects, 4.1% of participants had TPOAb greater than 200 IU/mL. The prevalence of goiter was 35.9%. An inhomogeneous echo pattern was detected in 35.2% and nodules in 20.2% of participants. Diffuse autoimmune thyroiditis was diagnosed in 47 subjects (1.2%). Conclusion: There are a number of thyroid disorders in this previously iodine-deficient region. Further studies are required to investigate the change of thyroid disorders duringiodine supplementation programs.

Introduction

IODINE DEFICIENCY is a risk factor for goiter, thyroid nodularity and hyperthyroidism (1). Iodine-induced hyperthyroidism occurs more often in regions of long-term iodine deficiency (2). Little is known about the prevalence of thyroid disorders after iodine supplementation in previously iodine-deficient regions.

West Pomerania, a region located in northeast Germany, was a previously iodine-deficient area with endemic goiter (3,4). The prophylactic procedures that were gradually introduced in 1983 were different between the eastern and western part of Germany. In East Germany, iodine supplementation was improved by mandatory iodine prophylaxis. However, after the reunification of Germany in 1989 and the adaptation of the “voluntary principle” the iodine intake decreased again (5). In December 1993, improved legislation concerning the iodization of table salt became effective. These changes contributed considerably to an increase in the use of iodized salt for food production. The median urinary iodine concentration in adolescents of the study area increased from 6.0 μg/dL in 1994 to 9.9 μg/dL in 1998 and to 12.0 μg/dL in 2000 (1). Furthermore, the increase of iodine content of food and breast milk (6), and the decrease of thyroid volume in adolescents (7,8) indicate the improved iodine supply. But the effect of long-term iodine supplementation on preexisting thyroid disorders is not well understood, especially in middle-aged and older people. Epidemiologic studies on evaluation of iodine supplementation programs are rare. Iodine prophylaxis programs were even suspected to cause iodine-induced hyperthyroidism in older people (9).

The aim of the present study was to analyze the current status of morphologic and functional thyroid abnormalities in West Pomerania as a previously iodine-deficient area.

Materials and Methods

The Study of Health in Pomerania (SHIP) is a cross-sectional epidemiologic survey in West Pomerania, a region in northeast Germany including the 3 cities of Greifswald, Stralsund, Anklam, and 29 surrounding communities (10). The
total population was 212,517 inhabitants. A two-stage cluster sampling method was adopted from the WHO MONICA Project Augsburg, Germany (11) and yielded twelve five-year age strata (20-79 years) for both genders, each including 292 individuals. Data collection started in October 1997 and was finished in March 2001. In all, 7008 people were invited to participate and 4310 (68.8% of eligible subjects) did. All participants gave written informed consent. The study was approved by the Ethics Committee of the University of Greifswald.

There were 349 (62 men and 287 women) of 4310 subjects with known thyroid disease. The disease was diagnosed within the past year in 50 of these participants (14.4%). Two hundred eighty persons (80.5%) reported taking thyroid medication (iodine, thyroid hormone replacement, suppression therapy, or thyrostatics). These individuals and an additional 20 participants (9 men and 11 women) with uncertainty regarding a possible thyroid disorder were excluded from further analysis. This resulted in a total study population of 3941 participants (2046 men and 1895 women) with no or undiagnosed thyroid disorders.

Sociodemographic characteristics and medical histories on thyroid disorders were assessed by computer-aided face-to-face interviews. Laboratory parameters were analyzed in a central laboratory. Spot urine samples of 3858 participants were collected and analyzed for iodine concentration by photometric procedure (Photometer ECOM 6122, Eppendorf, Hamburg, Germany) with Sandell and Kolthoff reaction (12). One hundred sixty-six of the 3941 participants had no blood drawn. Serum thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) levels were measured by immunocolumnescent procedures (FT3, LUMItest, Brahms, Berlin, Germany; TSH and FT4, LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany). The functional sensitivity of the TSH assay was 0.03 mIU/L. Reference ranges were: TSH, 0.3–3 mIU/L; FT4, 10–25 pmol/L; FT3, 3.4–7.1 pmol/L. Serum FT3 or FT4 levels were not available for 13 persons. Thyroid status was defined as follows: euthyroid, TSH, FT4, and FT3 levels within the normal ranges; decreased TSH level, TSH level less than 0.3 mIU/L; subclinical hyperthyroid, suppressed TSH level and FT4 and FT3 levels within the normal ranges; hyperthyroid, suppressed TSH level and FT4 greater than 25 pmol/L and/or FT3 greater than 7.1 pmol/L; subclinical hypothyroid, TSH level greater than 3 mIU/L and FT4 and FT3 levels within the normal ranges; hypothyroid, TSH level greater than 3 mIU/L and FT4 less than 10 pmol/L and/or FT3 less than 3.4 pmol/L.

Serum autoantibodies to thyroperoxidase (TPOAb) were measured by an enzyme immunoassay (VARELISA, Elias Medizintechnik GmbH, Freiburg, Germany). The functional sensitivity of this assay was 1 IU/mL. The normal range was less than 60 IU/mL for men and less than 100 IU/mL for women. TPOAb were not available in 16 subjects. The TPOAb status was defined as follows: normal, less than 60 IU/mL in men; less than 100 IU/mL in women; elevated, 60 IU/mL or more in men; or more 100 IU/mL in women; positive, greater than 200 IU/mL (13).

Thyroid ultrasonography was performed with an Ultrasound VST-Gateway with a 5-MHz linear array transducer (Diasonics, Santa Clara, CA) in 3915 participants. Thyroid volume was calculated as length × width × depth × 0.479 (mL) for each lobe (14). Goiter was defined as a thyroid volume exceeding 18 mL in women and 25 mL in men (15). The normal thyroid echo pattern was classified as homogenous. A homogeneous echo pattern with reduced echogenicity was defined as hypoechogenic. An autoimmune thyroiditis was assumed, if a hypoechogenic echo pattern of both thyroid lobes was combined with TPOAb positivity. If the echo pattern was not homogeneous, showing small lesions or distinct diffuse abnormalities in the echotexture of the gland, it was classified as inhomogeneous (14). Nodular changes exceeding 10 mm in diameter were defined as nodules.

Statistics

Data on quantitative characteristics are expressed as median and range. Data on qualitative characteristics are expressed as percent values or absolute numbers as indicated. Comparisons between groups were made using χ2-test (nominal data) or Mann-Whitney U test (interval data). Age-adjusted analyses were done by logistic regression. Odds ratio (OR) and its 95% confidence interval (95% CI) are given. A value of p < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (SPSS GmbH Software, Munich, Germany).

Results

We analyzed a final population of 3941 participants with no known thyroid disorders, between the ages of 20 and 79 years. Age and gender distributions were similar between 20 and 59 years of age. Above the age of 60 years, however, the number of subjects decreased progressively and because of the exclusion of individuals with known thyroid disorders and more women excluded from the analyses, there were relatively fewer women (by 29.7%) (Fig. 1).

The median iodine urine excretion was 12.4 μg/dL. An iodine excretion of less than 10 μg/dL was seen in 37% of participants and less than 5 μg/dL in 10.8%. Only 60 participants (1.5%) had an iodine urine excretion less than 2 μg/dL (Fig. 2). These data define the current status as a non-iodine–deficient area (16,17). There were no significant differences between the iodine urine concentration over the 4 years of study.

Four hundred twenty-eight of the 3775 participants with blood drawn (11.3%) had decreased serum TSH levels less than 0.3 mIU/L. The distribution of decreased serum TSH levels were age-dependent with higher percentages in older decades, but similar among women and men (Fig. 3). Suppressed TSH levels less than 0.1 mIU/L were found in 82 subjects (2.2%) without a clear gender-related trend. However, data obtained statistical significance for the increase with age.

Sixteen persons (8 women and 8 men) of the 82 subjects (19.5%) with suppressed serum TSH levels were hyperthyroid, 8 having elevated serum FT3 levels; 4, elevated serum FT4 levels; and 4, both increased serum FT3 and FT4 levels. The overall prevalence of overt hyperthyroidism was 0.4%, its distribution being age-dependent with a higher prevalence in older decades. The remaining 66 persons (1.8%) with suppressed TSH levels were classified as subclinical hyperthyroid. The distribution of subclinical hyperthyroidism was
also age-dependent with higher percentages in older decades but similar among women and men.

Forty-five of 3775 (1.2%) subjects had TSH levels greater than 3 mIU/L. There was no continuous age-dependent increase of elevated TSH levels. Increased TSH levels were more often detected in women compared to men \((p \text{ for pooled data } < 0.05; \text{ OR } 2.77; 95\% \text{ CI } 1.44–5.3)\). There were 18 persons (0.5%) with subclinical hypothyroidism. Among the 45 participants with elevated TSH levels there were 27 (0.7%) with overt hypothyroidism, 22 of them having decreased \(FT_4\) levels; 2, decreased \(FT_3\) levels; and 3, both decreased \(FT_4\) and \(FT_3\) levels. The prevalence of overt hypothyroidism was not age-dependent and was more common in women compared to men \((p \text{ for pooled data } < 0.05; \text{ OR } 3.2; 95\% \text{ CI } 1.35–7.61)\). Elevated TPOAb activities were found in 265 subjects (7.0%) (Fig. 4). The distribution of increased TPOAb activities was age- and gender-dependent with a higher prevalence in older decades and in women \((p \text{ for pooled data } < 0.05; \text{ OR } 2.49; 95\% \text{ CI } 1.91–3.26)\). A positive finding of TPOAb greater than 200 IU/mL was detected in 153 subjects (4.1%).

Goiter was diagnosed in 1414 subjects (35.9%) (Table 1). The prevalence of goiter increased with age \((p < 0.05)\). There was an age-adjusted tendency toward a higher prevalence of goiter in men compared to women \((p \text{ for pooled data } = 0.067; \text{ OR } 1.13; 95\% \text{ CI } 0.99–1.29)\). The median serum TSH was 0.51 mIU/L in subjects with goiter compared to 0.76 mIU/L in subjects without goiter \((p < 0.05)\).

The ultrasound investigation revealed 1389 positive findings (35.2%) of an inhomogeneous thyroid echo pattern (Table 1). An inhomogeneous thyroid echo pattern of the left lobe was diagnosed in 385 subjects and of the right lobe in 425 persons. Five hundred seventy-nine persons had an inhomogeneous echo pattern of both thyroid lobes. The distribution of this ultrasound finding was age-dependent with a higher prevalence in older age groups \((p < 0.05)\). Female subjects were more often affected than male participants \((p \text{ for pooled data } < 0.05; \text{ OR } 2.05; 95\% \text{ CI } 1.78–2.36)\). All par-

![FIG. 1. Age and gender distribution of the study population.](image)

![FIG. 2. The urine iodine excretion in the study population. The number of individuals per group is shown on the graphs. The rate of individuals per group is given in boxes.](image)
Participants with nodules were recommended to visit an endocrinologist for further diagnostic tests. Results of those tests, in particular data on the prevalence of definite thyroid cancer and its histologic classification were not available. Median serum TSH levels were not significantly different in subjects with an inhomogeneous echo pattern and in subjects with a homogenous echo pattern (0.62 mIU/L vs. 0.69 mIU/L; \( p < 0.05 \)). The goiter frequency was 44.8% in participants with an inhomogeneous thyroid echo pattern and 31.4% in subjects with a homogeneous echo pattern (\( p < 0.05 \)).

There were 791 participants (20.2%) with positive ultrasound findings of thyroid nodules (Table 1). In 267 persons nodules were detected within the left lobe and in 319 persons they were within the right lobe. Both lobes were affected in 205 participants. More women had nodules compared to men (\( p \) for pooled data < 0.05; OR 1.69; 95% CI 1.43–1.99). The prevalence of thyroid nodules increased with every decade of age (\( p < 0.05 \)). Subjects with nodules had a lower median TSH level (0.53 mIU/L) than subjects without thyroid nodules (0.7 mIU/L) (\( p < 0.05 \)). The prevalence of nodules in goiter was 62.7% vs. 29.4% in nongoiter persons (\( p < 0.05 \)).

A hypoechogenicity of both thyroid lobes was found in 182 subjects (4.6%) (Table 1). The prevalence was age-dependent with continuous increases over the decades (\( p < 0.05 \)).

FIG. 3. Decreased serum thyrotropin (TSH) levels with respect to age and gender. *\( p < 0.05 \).

FIG. 4. Elevated serum autoantibodies to thyroperoxidase (TPOAb) levels with respect to age and gender. *\( p < 0.05 \).
### Table 1. Thyroid Ultrasound Findings with Respect to Age and Gender

<table>
<thead>
<tr>
<th>Age group [years]</th>
<th>Goiter (n = 1414)</th>
<th>Inhomogeneous echo pattern (n = 1389)</th>
<th>Nodules (n = 791)</th>
<th>Hypoechoogenicity (n = 182)</th>
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<tr>
<td></td>
<td>Male (n = 776) [%]</td>
<td>Female (n = 638) [%]</td>
<td>Male (n = 600) [%]</td>
<td>Female (n = 789) [%]</td>
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</table>
0.05) but with a marked decrease in women older than 70 years. Women were more often affected than men ($p$ for pooled data $< 0.05$; OR $4.15$; $95\%$ CI $2.91$–$5.91$). The frequency of elevated TSH levels in subjects with and without hypoechogenicity of both thyroid lobes was $11.7\%$ vs. $0.7\%$ ($p < 0.05$), the frequency of elevated TPOAb $26.3\%$ vs. $3.0\%$ ($p < 0.05$). Diffuse autoimmune thyroiditis as defined by the presence of hypoechogenicity and TPOAb positivity was detected in 47 subjects ($1.2\%$; 45 women and 2 men). The functional status of these participants was as follows: 13 subjects ($27.7\%$) were hypothyroid, 3 ($6.4\%$) subclinically hypothyroid, $30$ ($63.8\%$) euthyroid, and $1$ ($2.1\%$) subclinically hyperthyroid. Goiter was present in 9 of these participants ($19.1\%$).

**Discussion**

The present study is a cross-sectional survey of thyroid abnormalities in a previously iodine-deficient area. The current median iodine urine excretion shows that the iodine supplementation is now effective. However, there is still a relevant fraction of participants with low and very low urinary iodine levels indicating an insufficient iodine supply in those people and a suboptimal current iodine supplementation in the studied region.

There are three explanations for the high prevalence of decreased serum TSH of $11.3\%$ in all participants and of approximately $20\%$ in older decades. First, because of prior iodine deficiency, older subjects especially had a significantly higher rate of nodularity with a hypothesized relevant part of autonomous thyroid adenomas included. Second, because older subjects more frequently had positive antibodies, Graves’ disease may have caused decreased serum TSH levels. However, there were only 17 of 385 participants ($4.4\%$) with decreased serum TSH who were also positive for TPOAb, excluding an effect of Grave’s disease relevant for these population-based findings. Third, the lower TSH limit of $0.3$ mIU/mL may have been responsible for the high prevalence of decreased serum TSH levels. The border line low TSH level used in population based or epidemiological studies ranges from the functional sensitivity of the used assay (18) to $0.4$ mIU/mL (19) indicating the need for international standardization.

Subclinical and overt hyperthyroidism were defined by further measurement of elevated FT$_3$ and/or FT$_4$ levels. There are few population-based studies (13,19,20) that have been performed with this intensive approach. The prevalence of hyperthyroidism of $0.64\%$ found here was similar to that reported for areas with sufficient iodine supplementation (18,21) and mild iodine-deficient areas (13), whereas relevant hyperthyroidism could be detected in up to $2.9\%$ of all cases in moderately iodine-deficient areas (22).

Women more often had thyroid nodules than men. However, there was no gender-related trend for decreased and suppressed serum TSH as well as for subclinical and overt hyperthyroidism, and even a tendency towards a higher goiter prevalence in men. This might be related to selection of the study population that only comprised participants with as yet undiagnosed thyroid disorders. Females were more often excluded because of a known thyroid disorder than male participants. Thus, these findings may be explained by an earlier diagnosis of subclinical and overt hyperthyroidism in women compared to men.

The low prevalence of hypothyroidism in our population is consistent with other studies from low to normal dietary iodine uptake (13,23). An epidemiologic study from southern Germany (20) also revealed a prevalence of hypothyroidism of $0.7\%$ in people with as yet no known thyroid diseases. Studies performed in areas with high iodine uptake (18,21,24) revealed a prevalence of hypothyroidism from $0.4\%$ (25) up to $4.6\%$ (18). In contrast to other studies (18,19) the distribution of hypothyroidism was not age-dependent and even showed a small decline in older age decades. This finding should be interpreted with caution, because it is from a cross-sectional study.

Positive findings of TPOAb were more often found in older persons and were more prevalent in women and in subjects with hypothyroidism. These results are consistent with other studies (13,18,22,25,26). We differentiated between elevated and positive TPOAb findings, because it could be shown, that TPOAb levels greater than $200$ mIU/mL are much better associated with thyroid dysfunction than mildly increased TPOAb levels (13).

Epidemiologic data on autoimmune thyroiditis defined by combined characteristics of ultrasound and serum TPOAb are rare. Aghini-Lombardi and coworkers (22) found an autoimmune thyroiditis prevalence of $3.5\%$ in an Italian iodine-deficient community. Iodine deficiency increases the risk of goiter and this may overexpose the immune system to thyroid antigens, leading to humoral and cell-mediated reactions that result in an elevated prevalence of autoimmune thyroiditis (22). Thus, the lower prevalence in our study may be related to the improved iodine supplementation.

The prevalence of thyroid nodules of $20.2\%$ is consistent with the prevalence found in other study regions (27–31). Data from prospective studies (32,33) showed an annual growth of thyroid nodules of approximately $10\%$. This growth rate could not be decreased by use of iodide and/or levothyroxine (34). This suggests that further improvement of iodine supply will probably not diminish the nodule prevalence in older decades. However, the high prevalence of nodules in contrast to the low prevalence of overt hyperthyroidism may indicate a beneficial functional effect of nutritional iodization.

The prevalence of goiter in people with as yet unknown thyroid disorders was $35.9\%$. Ultrasound studies from Germany in adults revealed a goiter prevalence of $42.6\%$ (27) and $49.7\%$ (28). Differences may result from selection bias. One study performed was clinical based (27) and the other in elderly subjects older than 60 years (28). The lower goiter prevalence in our study area may also reflect the first positive effects of an effective iodine food supplementation. It has been shown that the goiter prevalence decreased from $36\%$ in 1992 to $9\%$ in 1998 in adolescents aged 11 to 17 years in the SHIP region (7). Other studies (8,34) from neighboring regions confirmed these findings. The goiter prevalence of $15\%$ in the 20 to 29-year-age group of the SHIP population and the low goiter prevalence in individuals younger than 40 years reported from Austria (35) correspond with these results. The high goiter prevalence in older people indicates that a generation is probably needed to eradicate endemic goiter by salt iodization.

A limitation of this cross-sectional study is that it does not allow the evaluation of changes in thyroid disorders by comparing the situation “before” (when iodine deficiency was


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