CLINICAL STUDY

Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status

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Abstract

Objective: The pattern of thyroid dysfunction seems to depend on the iodine status of the population. Prevalence of thyroid dysfunction could be a parameter to consider when evaluating iodine deficiency disorders in a population.

Design: Comparative cross-sectional investigation in two regions in Denmark with marginally different iodine excretion.

Methods: A random selection of 4649 participants from the Civil Registration System in Denmark in age groups between 18 and 65 years were examined. Thyroid dysfunction was evaluated from blood samples and questionnaires, and compared with results from ultrasonography.

Results: Median iodine excretion was 53 µg/l in Aalborg and 68 µg/l in Copenhagen. Previously diagnosed thyroid dysfunction was found with the same prevalence in the regions. Serum TSH was lower in Aalborg than in Copenhagen ($P=0.003$) and declined with age in Aalborg, but not in Copenhagen. Not previously diagnosed hyperthyroidism was found with the same overall prevalence in the regions, but in age >40 years hyperthyroidism was more prevalent in Aalborg (1.3 vs 0.5%, $P=0.017$). Not previously diagnosed hypothyroidism was found more frequently in Aalborg (0.6 vs 0.2%, $P=0.03$). Hyperthyroidism was more often associated with macronodular thyroid structure at ultrasound in Aalborg and hypothyroidism was more often associated with patchy thyroid structure in Copenhagen.

Conclusions: Significant differences in thyroid dysfunction were found between the regions with a minor difference in iodine excretion. The findings are in agreement with a higher prevalence of thyroid autonomy among the elderly in the most iodine-deficient region.

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Introduction

It has previously been demonstrated that the pattern of thyroid dysfunction is different in areas with clear iodine repletion and moderate iodine deficiency (1). In iodine-replete areas, a higher incidence of sub-clinical and overt hypothyroidism is found, whereas sub-clinical and overt hyperthyroidism is found with a higher incidence in iodine-deficient areas, especially among the elderly. An ecological comparison of previous population-based studies from a recent review (2) does not unambiguously lead to the same conclusion, partly because of methodological differences, partly because most studies were conducted in iodine-replete areas. Recent studies from iodine-deficient (3, 4) and mildly

iodine-deficient areas (5) confirmed the tendency towards higher prevalences of hypothyroidism in iodine repletion and higher prevalences of hyperthyroidism in iodine deficiency when compared with previous studies.

Hyperthyroidism in iodine deficiency is believed to be associated with thyroid autonomy with a high prevalence of thyroid nodules, whereas autoimmunity is more often the cause of hyperthyroidism – Graves' disease – in iodine-replete areas (6). Consequently, hyperthyroidism has a lower age of onset in iodine-sufficient areas, as Graves' disease is seen mostly in the young and middle-aged, whereas toxic nodular goitre is primarily seen among the elderly. The high incidence of hypothyroidism in iodine repletion may be due to an

increased prevalence of thyroid autoimmunity (7, 8) as well as an increased susceptibility to hypothyroidism in cases with thyroid autoimmunity (1, 9, 10).

With our comparative design, we could avoid bias caused by differences in methodology, different principles of classification, and differences in the composition of the cohort. Thus, we could analyse differences in the prevalences of thyroid disorders attributed to the difference in iodine excretion in the two areas with mild and moderate iodine deficiency. Further, we wanted to compare thyroid dysfunction in the two areas with thyroid structure at ultrasonography.

Materials and methods

In the period between March 1997 and June 1998, a random sample of the population was examined within the groups: women aged 18–22, 25–30, 40–45 and 60–65 years and men aged 60–65 years. The cohort was drawn from the Civil Registration System in which all subjects living in Denmark are registered, and subjects were included from the north-western part of the municipality of Copenhagen and the central part of Aalborg, a city in the north-western part of Denmark. These regions were chosen as previous studies have demonstrated a difference in iodine excretion between the regions (5, 11) probably conditioned by different iodine content of drinking water (12). Otherwise, the regions are comparable as they are both urban areas and no major differences in genetic background should be present. In total, 40 233 subjects were included in the sample, and they were all given random numbers within the groups by a PC program and subsequently invited in the order of the random numbers until the desired number of participants in each group was obtained.

The subjects were asked to participate by letter, and in case of no response another letter was sent. If there was still no response or the participants refused to participate in the full examination, they were asked to answer a short questionnaire concerning, among other things, previous thyroid disease and familial occurrence of thyroid disease.

The participants answered questionnaires concerning previous thyroid disease, familial occurrence of thyroid disease and medication. At the investigation, further information was obtained in an interview with an MD, and if there was still uncertainty about previous thyroid disease, medical records were traced.

Blood samples were drawn and stored at -20°C , and subsequently the samples were analysed in a sequence ensuring that samples were mixed with respect to region, age, sex and season. Serum thyrotrophin (TSH), free thyroxine (fT_4) and free tri-iodothyronine (fT_3) concentrations were analysed with LUMitest (BRAHMS, Berlin, Germany). The functional sensitivity of the TSH assay was 0.01 mU/l. For comparison of sub-clinical thyroid dysfunction between the regions, a reference interval for serum TSH was defined as 0.4–3.6 mU/l,

corresponding to the 2.5th and 97.5th percentiles of TSH among participants with no known thyroid disease, TPO Ab < 60 kU/l (Dynotest RIA, BRAHMS), no thyroid enlargement, and no thyroid nodules at ultrasonography. The reference interval for serum TSH for the detection of overt thyroid dysfunction was set to 0.2–5.0 mU/l, corresponding to the interval used in daily clinical practice and to limits most often used in other epidemiological surveys to allow comparisons. Reference intervals for fT_3 and fT_4 were defined as 2.5th to 97.5th percentiles after exclusion of participants with known thyroid disease or serum TSH outside the reference interval, resulting in a reference interval of 9.8–20.4 pmol/l for fT_4 and 3.6–6.9 pmol/l for fT_3 . Consequently, euthyroidism was defined as a serum TSH concentration in the range 0.4–3.6 mU/l. Sub-clinical hyperthyroidism was defined as a serum TSH < 0.4 mU/l and no overt hyperthyroidism defined as TSH < 0.2 mU/l and fT_3 > 6.9 pmol/l or TSH < 0.2 mU/l and fT_4 > 20.4 pmol/l. Sub-clinical hypothyroidism was defined as serum TSH > 3.6 mU/l and no overt hypothyroidism defined as serum TSH > 5 mU/l and fT_4 < 9.8 pmol/l.

Thyroid ultrasonography was performed with a Siemens Sonoline Versa Pro with a 7.5 MHz 70 mm linear transducer, effective length 62 mm (Siemens, Erlangen, Germany). Thyroid volume was calculated as $\text{length} \times \text{width} \times \text{depth} \times \pi/6$ for each lobe. Thyroid nodules exceeding 5 mm in diameter were registered; in cases of more than three nodules in a lobe, only the three largest were registered. The thyroid echo pattern was classified as diffuse or patchy. An evaluation of the inter-observer variation of these variables showed good agreement for thyroid volume and number of nodules, but little agreement for echo pattern (13). Echo pattern was consequently only used for comparisons within each region.

Casual urine samples were collected during the time interval 0800 to 1900 h and analysed for iodine concentration by the Ce/As method after digestion by alkaline ashing as previously described (14, 15). The median iodine excretion was 53 $\mu\text{g/l}$ (0.42 $\mu\text{mol/l}$) in Aalborg and 68 $\mu\text{g/l}$ (0.54 $\mu\text{mol/l}$) in Copenhagen (Fig. 1); after exclusion of subjects taking individual iodine supplementation the figures were 45 $\mu\text{g/l}$ (0.35 $\mu\text{mol/l}$) and 61 $\mu\text{g/l}$ (0.48 $\mu\text{mol/l}$) respectively. According to WHO criteria (16), the Aalborg region can be classified as moderately iodine-deficient and the Copenhagen region can be classified as mildly iodine-deficient.

The study was approved by the regional Ethics Committee in Copenhagen and Northern Jutland and all participants gave written informed consent.

Statistics

Data processing was done with SPSS version 8.0 software. Non-parametric statistics were used for the analysis of continuous data (Mann–Whitney and

Figure 1 The distribution of iodine concentrations in spot urine samples from subjects in two regions in Denmark. Urine samples were available from 4616 participants (99.3%). Boxes represent median and inter-quartile range; whiskers represent 10th and 90th percentiles. *P* for regional difference <0.001 (Mann–Whitney).

Kruskal–Wallis), and general linear models were used to analyse the relation between a dependent and more than one independent variable; logarithmic transformation was then used for continuous variables. For the TSH analyses data were adjusted for the sampling hour, as the age and sex groups were not equally distributed throughout the day and serum TSH varied through the day. For dichotomous variables Pearson Chi square tests and logistic regression analysis were used. An interaction parameter was included in the logistic regression analyses to test for differences in the relative distribution of a variable between the regions. The level of significance was set to 5%.

Results

Participation

The participation rate was 50.1%, as 4649 subjects participated out of the 9274 invited. The short questionnaire was answered by another 26.8% and 23.1% did not respond. The participation rate was higher in Aalborg than in Copenhagen (54.6 vs 46.6%, $P < 0.001$), and the short questionnaire was answered by the same fraction of the cohort in the two regions (26.5 vs 27.0%). Results from the thyroid function tests were available on 4583 subjects (98.6%) and results from the ultrasound investigation were available on 4642 subjects (99.8%).

In a comparison of self-reported thyroid dysfunction among participants and responders to the short questionnaire only (non-participants), no significant differences were found between participants and

non-participants for hyperthyroidism (participants 2.4%, non-participants 1.8%, non significant) or hypothyroidism (participants 2.9%, non-participants 2.8%, non significant), whereas bias was found regarding self-reported goitre (5.9% vs 3.6%, $P < 0.001$). Familial occurrence of thyroid dysfunction was also reported more often by participants (8.0%) than non-participants (4.8%), $P < 0.001$; however, only minor difference in the prevalence of thyroid dysfunction in this study was found between participants with or without familial occurrence of thyroid disease (1.4% vs 1.1%). No differences in the degree of selection bias were found between the regions.

Previously diagnosed thyroid dysfunction

To the question, 'has a doctor ever told you that you had hyperthyroidism?', 133 answered yes, but after the interview and tracing of medical records, the number of participants with previous hyperthyroidism was 101 (92 cases confirmed and nine additional cases identified), yielding a prevalence of previously diagnosed hyperthyroidism of 2.2%. To the corresponding question concerning hypothyroidism, positive answers were given in 109 cases. After the interview only 53 cases were confirmed and another seven cases were identified, yielding a prevalence of previously diagnosed hypothyroidism of 1.3%.

The prevalence of previously diagnosed hyperthyroidism was 1.9% in mild iodine deficiency (ID) and 2.5% in moderate ID, and the prevalence of hypothyroidism was 1.2% in mild ID and 1.4% in moderate ID. The prevalence of previously diagnosed thyroid dysfunction was obviously increasing with age, but no significant regional differences were found overall or in any of the age groups. Two cases of thyroiditis and two cases of thyroid cancer had been diagnosed in each region.

Thyroid function tests

Serum TSH concentrations showed significant regional differences caused by a decline in TSH with age in the moderate ID area, a decline that was not present in the mild ID area (Table 1). A significant regional difference in TSH among the elderly men also contributed to the overall regional difference in TSH. If an adjustment for the nodularity of the thyroid was introduced in the analysis, the regional differences in TSH were only seen in subjects with nodular glands, whereas subjects without nodules had similar TSH levels in the two regions ($P = 0.002$ for interaction in a linear model). No significant overall regional difference was found for serum fT_3 or serum fT_4 . A parallel decline from 5.28 to 5.10 pmol/l (median) in free T_3 ($P < 0.001$, linear model) and increase in free T_4 from 13.9 to 15.2 pmol/l ($P < 0.001$) with age among women was found in the two regions (data not shown).

Table 1 Mean serum TSH after logarithmic transformation in 4356 participants never treated for thyroid disease from two regions in Denmark with mild (Copenhagen) and moderate (Aalborg) iodine deficiency. Serum TSH values correspond to morning values. *P* values for the regional difference and the difference between age groups in linear models are given. Values in parentheses are 95% confidence intervals for the mean.

Sex and age	TSH mild ID mU/l (95% CI)	TSH moderate ID mU/l (95% CI)	<i>P</i> (between regions)
Women, 18–22	1.44 (1.35–1.55)	1.49 (1.38–1.60)	0.62
Women, 25–30	1.49 (1.39–1.60)	1.40 (1.30–1.52)	0.26
Women, 40–45	1.39 (1.29–1.50)	1.27 (1.17–1.37)	0.05
Women, 60–65	1.31 (1.21–1.42)	1.14 (1.05–1.25)	0.004
Men, 60–65	1.36 (1.27–1.47)	1.23 (1.13–1.43)	0.04
Total	1.40 (1.33–1.47)	1.31 (1.25–1.37)	0.004
<i>P</i> (between groups)	0.15	<0.001	

Not previously diagnosed thyroid dysfunction

The prevalence of thyroid dysfunction among participants who had never been treated for thyroid disease is illustrated in Table 2. The prevalence of hyperthyroidism as well as hypothyroidism including sub-clinical disease was increasing with age ($P < 0.001$, Pearson Chi-square) and the prevalence was higher among women than among age-matched men ($P < 0.001$). Not previously diagnosed hyperthyroidism was found with the same prevalence in the two regions when all age groups were included. The tendency was that hyperthyroidism was diagnosed more often in the younger age groups in mild ID ($P = 0.057$), and conversely a significantly higher prevalence of not previously diagnosed hyperthyroidism was found in moderate ID among participants aged more than 40 years ($P = 0.017$). Combining the cases with previous and present thyroid dysfunction did not yield further statistically significant regional differences. When all age groups were included, a small difference in the prevalence of sub-clinical hyperthyroidism was found ($P = 0.049$). When only subjects over the age of 40 years were included, the regional difference in sub-clinical hyperthyroidism was more pronounced (7.8% in moderate ID vs 5.3% in mild ID, $P = 0.01$).

The prevalence of overt hypothyroidism was higher in moderate ID than in mild ID ($P = 0.03$) (Table 2). Though a tendency was seen towards a higher prevalence of sub-clinical hypothyroidism in mild ID than in moderate ID in subjects aged 40 years or more (5.4 vs 4.0%, $P = 0.097$), no significant differences in the prevalence of sub-clinical hypothyroidism were found.

For comparison with other studies, sub-clinical hyperthyroidism was also computed as $TSH < 0.2$ mU/l, which was found in 1.8% in mild ID and 2.0% in moderate ID ($P = 0.64$); and sub-clinical hypothyroidism was defined as $TSH > 5$ mU/l, which was found in 2.0% in mild ID and 1.8% in moderate ID ($P = 0.69$).

Thyroid dysfunction and thyroid structure

Thyroid structure at ultrasound in different groups of thyroid function is demonstrated in Fig. 2. Macronodular thyroid structure was found in 75.9% of participants with suppressed TSH (< 0.2 mU/l) and in 27.8% of participants with normal TSH (OR 3.7; CI 2.0–6.8 in a logistic regression analysis adjusting for the possible confounding by age). Correspondingly, thyroid enlargement defined as a thyroid volume exceeding 18 ml for women and 25 ml for men (17) was found in 63% of participants with suppressed TSH, in 17% of participants with normal TSH, and in 10% of participants with elevated TSH.

Likewise, patchy thyroid structure at ultrasound was found in 51.8% of participants with elevated TSH and in 13.5% participants with normal TSH (OR 6.2; CI 4.0–9.8 in logistic regression analysis adjusting for age and sex).

Discussion

In this study, comparisons in a Danish cohort are made between two regions that differ slightly with respect to iodine excretion but that are otherwise comparable. This regional difference in iodine excretion has been relatively constant since the first major investigation more than 30 years ago (11). No differences were found in the prevalence of previously diagnosed thyroid dysfunction in any age group, but some differences in the prevalence of not previously diagnosed thyroid dysfunction were found.

Serum TSH levels differed significantly between the regions. Lower levels of TSH were found in the moderate ID area than in the mild ID area due to a decline in TSH with age in moderate ID, a decline not observed in mild ID. In an iodine-sufficient area in Sweden, TSH increased with age, though the difference was not significant (18), and in an iodine-deficient area in Italy, an age-related decline in TSH has been reported (4). In a

Table 2 Thyroid function in 4360 participants never treated for thyroid disease in two areas in Denmark with mild (Copenhagen) or moderate (Aalborg) iodine deficiency.

Sex and age	Hyperthyroid		Sub-clinical hyperthyroid		Euthyroid		Sub-clinical hypothyroid		Hypothyroid		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
<i>Mild ID</i>												
Women, 18–22	1	0.2	13	2.7	459	94.6	12	2.5	0		485	100.0
Women, 25–30	3	0.6	11	2.3	447	92.2	22	4.5	2	0.4	485	100.0
Women, 40–45	2	0.4	17	3.7	421	90.9	22	4.8	1	0.2	463	100.0
Women, 60–65	4	1.0	28	7.3	319	82.6	34	8.8	1	0.3	386	100.0
Men, 60–65	0		19	4.0	442	93.3	13	2.7	0		474	100.0
Total	10	0.4	88	3.8	2088	91.1	103	4.5	4	0.2	2293	100.0
<i>Moderate ID</i>												
Women, 18–22	0		11	2.5	412	93.0	16	3.6	4	0.9	443	100.0
Women, 25–30	0		11	2.5	410	94.2	12	2.8	2	0.5	435	100.0
Women, 40–45	3	0.7	20	5.0	372	92.1	9	2.2	0		404	100.0
Women, 60–65	11	3.1	28	8.0	284	80.8	25	7.1	4	1.1	352	100.0
Men, 60–65	2	0.5	29	6.7	393	90.7	7	1.6	2	0.5	433	100.0
Total	16	0.8	99	4.8	1871	90.5	69	3.3	12	0.6	2067	100.0

Regional differences in total prevalences were analysed with Chi-square tests: $P=0.15$ for hyperthyroidism; $P=0.049$ for sub-clinical hyperthyroidism; $P=0.21$ for sub-clinical hypothyroidism; $P=0.03$ for hypothyroidism.

comparative study, higher median TSH was reported in an iodine-replete area than in an iodine-deficient area (19). Thus, in moderate iodine deficiency, a reduced serum TSH is observed compared with serum TSH in areas with a lesser degree of iodine deficiency or iodine sufficiency. These reduced TSH levels especially among the elderly are in contrast to increased TSH as a direct

effect of iodine deficiency as observed in severe iodine deficiency (20). This is presumably due to autonomous functioning thyroid tissue, as this regional difference in serum TSH was only found in subjects with nodular glands, and it is in accordance with data from moderate iodine deficiency in Italy, where decreasing levels of serum TSH were found with increasing degrees of goitre at a clinical examination (21).

A decline in serum TSH with age corresponds to the finding of an increased prevalence of overt as well as sub-clinical hyperthyroidism among the elderly in moderate ID. Likewise, not previously diagnosed overt hypothyroidism was more prevalent in moderate ID than in mild ID; it should be emphasized, however, that this difference is based on few cases. The major difference in thyroid dysfunction between iodine-deficient and iodine-replete areas has been reported in the older age groups (6). This is in accordance with an increasing prevalence of toxic nodular goitre with age in this study, especially in moderate ID. Consequently, if older age groups had been investigated, regional differences might have been more pronounced. That is, however, not possible in a set-up like ours, as participation rates would be too low and selection of the healthiest would occur to a large extent.

Our data indicate that, apart from a reduction in non-toxic goitre, a reduction in hyperthyroidism may be expected in the long run among the oldest part of the population following an increase in the iodine intake of a population as reported from other countries, though a temporary increase in the incidence of thyrotoxicosis has been reported from most studies after the initiation of iodization programmes (22–24).

Figure 2 Thyroid structure stratified by TSH level and region in 4357 subjects from two areas in Denmark with mild (Copenhagen) and moderate (Aalborg) iodine deficiency. Subjects with known thyroid disease were excluded. H = High TSH (>5 mU/l), N = Normal TSH (0.2 – 5 mU/l), L = Low TSH (<0.2 mU/l). Interaction terms in a logistic regression analysis were used to describe regional differences; suppressed TSH was more closely associated with macronodular thyroid structure in moderate ID than in mild ID ($P=0.02$), and elevated TSH was more closely related to patchy thyroid structure in mild ID than in moderate ID ($P=0.02$).

Comparisons of prevalences with previous studies is problematic due to the composition of this cohort with respect to age and sex and differences in the definitions of thyroid dysfunction. By selecting the relevant strata and paying attention to different cut-off levels for TSH, some comparisons could be made. Elevation of serum TSH was less common in our study than reported in most studies from iodine-replete areas in a recent review (2), and more common than in an iodine-deficient area (3). Suppressed TSH, on the other hand, seems less common than in iodine-deficient areas and more common than in iodine-replete areas as discussed in a previous paper (5).

When previously diagnosed thyroid disease is compared, the registration procedure needs to be accounted for. We found a considerable over-reporting of thyroid dysfunction in the questionnaires compared with data obtained from interviews and tracing of records, though only cases diagnosed by a physician were asked for in the questionnaire. Hyperthyroidism was over-reported by 32% and hypothyroidism by 82%, probably because weight problems are often attributed to thyroid dysfunction. Tunbridge *et al.* described a similar over-reporting of hyperthyroidism and a smaller over-reporting of hypothyroidism (25).

The participation rate in the full investigation was only 50% in this study, but no selection bias seemed to be present. Though bias might be caused by an over-representation of subjects with familial occurrence of thyroid dysfunction or with goitre among the participants, it was of little importance, as especially familial occurrence of thyroid disease was not a strong predictor of thyroid dysfunction, and as self-reported thyroid dysfunction was equally present among participants and responders to a short questionnaire only. Further, it should be emphasized that comparisons between the regions seemed unbiased, as no signs of difference in selection bias between the regions were found.

In conclusion, hyperthyroidism has a different age of onset in the two regions. A higher prevalence of not previously diagnosed hyperthyroidism was found in the area with the lowest iodine excretion due to an increased prevalence of hyperthyroidism in the oldest age groups. Corresponding to this, a decline in serum TSH and increased nodularity among participants with suppressed TSH was found in the region with the lowest iodine excretion, supporting the theory of increased autonomy in iodine-deficient areas.

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