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Iodine Intake and the Pattern of Thyroid Disorders: A Comparative Epidemiological Study of Thyroid Abnormalities in the Elderly in Iceland and in Jutland, Denmark

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ABSTRACT

Thyroid abnormalities are common in all populations, but it is difficult to compare results of epidemiological studies, because different methods have been used for evaluation. We studied the importance of the population iodine intake level for the prevalence rate of various thyroid abnormalities in elderly subjects.

Random samples of elderly subjects (68 yr) were selected from the central person registers in Jutland, Denmark, with low (n = 423) and, in Iceland, with longstanding relatively high (n = 100) iodine intake.

Females from Jutland had a high prevalence of goiter or previous goiter surgery (12.2%), compared with males from Jutland (3.2%) and females (1.9%) and males (2.2%) from Iceland. Abnormal thyroid function was very common in both areas, with serum TSH outside the reference range in 13.5% of subjects from Jutland and 19% of those from Iceland. In Jutland, it was mainly thyroid hyperfunction (9.7% had low, 3.8% had high serum TSH), whereas in Iceland, it was impaired thyroid function (1% had low, 18% had high serum TSH). All subjects with serum TSH more than 10 mU/L had autoantibodies in serum, but antibodies were, in general, more common in Jutland than in Iceland.

Thus, thyroid abnormalities in populations with low iodine intake and those with high iodine intake develop in opposite directions: goiter and thyroid hyperfunction when iodine intake is relatively low, and impaired thyroid function when iodine intake is relatively high. Probably, mild iodine deficiency partly protects against autoimmune thyroid disease. Thyroid autoantibodies may be markers of an autoimmune process in the thyroid or secondary to the development of goiter. (*J Clin Endocrinol Metab* **83:** 765–769, 1998)

THYROID abnormalities affect a considerable proportion of all populations (1). Autopsy studies have shown immune processes in the thyroid gland in 40–50% of elderly Caucasian women (2), and thyroid antibodies can often be demonstrated in serum (3, 4). The most common disease caused by thyroid autoimmunity is thyroid failure, ranging from subclinical hypothyroidism with slightly elevated serum TSH and questionable symptoms, to severe myxoedema. Graves' disease, caused by stimulating TSH receptor antibodies, is another prominent manifestation of thyroid autoimmunity.

The other major thyroid abnormality is autonomous nodular growth and function of the gland. The exact mechanism leading to this often multifocal process is unknown (5), but it is facilitated by a low iodine intake or an intake of goitrogens, which inhibit the thyroidal use of iodine. In iodine-deficient populations, goiter may affect more than half of the population, and autonomous function of thyroid nodules is the major cause for hyperthyroidism (6). It may take many years before a major change in the iodine intake is followed by a new steady pattern of thyroid disease (7, 8).

We performed comparative studies of thyroid abnormalities in Iceland and in Jutland, Denmark, to evaluate the effect of differences in population iodine intake on the prevalence rate of various thyroid disorders in the elderly. These areas have similar levels of medical care and socioeconomic development and a similar genetic background (9). The levels of iodine intake (low in Jutland, high in Iceland) have been relatively stable during the lifetime of the inhabitants (10, 11). A previous study showed profound differences in the pattern of diseases causing hyperthyroidism and the ages at manifestation (12). Now, major differences were demonstrated in the prevalence rate of abnormalities in thyroid function. The results suggest that, even in areas without goiter endemia, the population iodine intake level is a major determinant of which types of thyroid abnormalities are common.

Subjects and Methods

Populations

The populations studied were elderly subjects living in Iceland (Reykjavik and surroundings) and Jutland, Denmark (Randers and surroundings). Randers is a city of 56,000 inhabitants in East Jutland. Selection took place from the central person registers. For practical reasons, the investigation in Iceland included a random sample of 66- to 70-yr-old subjects (n = 100, males/females = 46/54, mean age 68 yr) also invited to participate in a population survey of heart diseases (n = 3,000), whereas in Jutland (n = 423, males/females = 185/238), it was all subjects in the municipality being 68 yr. In both areas, approximately 70% of the subjects invited to participate accepted the invitation. Hence, both groups were random population samples, with no special selection,

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apart from the necessary acceptance of participation. The investigation involved an interview on previous or present thyroid disease, past and actual smoking habits, pregnancies, health state and medication, possible sources of extra iodine intake, duration of habitation in the areas, goiter evaluation, and sampling of blood and urine. The majority had lived in the areas for more than 30 yr (Iceland 82%, Jutland 77%), and a large part of the remaining group had lived in other areas of Iceland and Jutland with similar levels of iodine intake. All were Caucasian. The number of smokers or previous smokers (Iceland males/females = 74/59%), Jutland males/females 48/43%), and the number of child births in women (Iceland 3, Jutland 2, medians) were moderately higher in Iceland than in Jutland.

Goiter evaluation

A clinical examination was performed for the presence of goiter, using a simplified score, where 0 was no goiter, I was an enlarged thyroid visible with extended neck or as judged from palpation, II was an easily depictable and clearly enlarged thyroid with the head in normal position, and III was a large goiter visible at a distance. The relevance of the distinction between grades 0 and I was tested in a control study. A random sample of participants from Jutland (n = 106) subsequently had thyroid volume measured by ultrasound (13) by a trained radiologist unaware of the initial score. Many had a relatively large thyroid volume without clinical goiter, but thyroid volume was not different in subjects with score 0 *vs.* score I (Fig. 1). Hence, only subjects with score II or III were considered to have goiter.

Laboratory procedures

Iodine was measured in morning spot urine samples in all subjects, to evaluate the possibility of excessive iodine intake as the cause for an elevated serum TSH. The concentrations were as expected: higher in Iceland [150 μg/L (33–703), median, range, n = 89] than in Jutland [38 μg/L (6–770), n = 197] in subjects with no extra iodine intake, as judged from history ($P < 0.01$). Subjects with intake of iodine containing medication or supplements of any kind and subjects with recent radiographic investigations involving iodine containing contrast media were excluded for this calculation. It reflects the basic iodine intake of the elderly population from the two areas. Iodine measurements were performed in duplicate as previously described (14). The recovery rate was more than 95%. Intra- and interassay coefficients of variation were 2.1 and 2.7%, respectively, and the detection limit in the setup used was 3 μg/L.

Blood samples were obtained during the time interval 0900–1600 h. Serum was stored at −20 C until analyses. Reagents for measurements of total T_4 (RIA, reference range 60–140 nmol/L) and T_3 (RIA, 1.2–2.7 nmol/L), and T_3 uptake test (0.8–1.2) were supplied by Farmos (Turku, Finland). T_3 Uptake test results were used to test for abnormalities in thyroid hormone binding proteins giving misleading T_4 and T_3 values (outside the reference range in euthyroid subjects or normal in hypo- or hyperthyroid subjects). No such abnormalities were found. TSH was measured by an immunoluminometric assay (Behring Werke, Marburg, Germany; detection limit 0.01 mU/L; reference range 0.40–4.0 mU/L). Characteristics of the assay have been given previously (15). Thyroid peroxidase antibodies (TPO-Ab) were measured by a very sensitive enzyme-linked immunosorbent assay [detection limit 4 U/L (reference standard code 66/387 NIBSC, London, UK)] using purified human TPO as antigen (4), thyroglobulin antibodies (Tg-Ab) by a very sensitive radioimmunoprecipitation assay (detection limit 20 U/L, reference standard code A 65193) (3), and Tg by an immunoluminometric assay (Behring Werke; detection limit <1 μg/L) including recovery measurements. Because Tg-Ab may influence Tg values (16), only samples with Tg-Ab values less than 200 U/L were used. No difference was found in subjects without Tg-Ab and with Tg-Ab [20–200 U/L; median Tg 13.1 (n = 390) *vs.* 14.3 μg/L (n = 50)]. During sampling, handling, transport, and storage of samples and during all analyses, special care was taken to avoid bias which could lead to spurious systematic differences between areas. For this purpose, all single runs of all assays included shifting groups of samples from both areas.

The Medstat program version 2.12 (Astra Albertslund, Denmark) was employed for calculation of medians and for statistical analyses (χ^2-test).

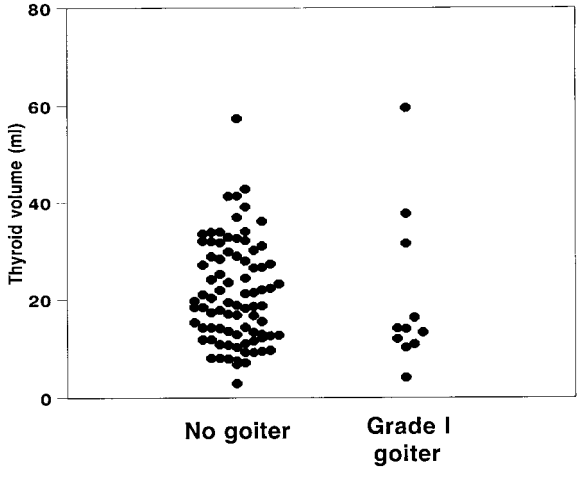

FIG. 1. Thyroid volume in 84 subjects from Jutland with no clinical goiter, and 11 rated to have goiter grade I. Two subjects with goiter grade II had volumes of 36.3 and 43.2 mL; 2 with grade III, 125 and 155 mL. Seven subjects had extension of the thyroid behind the sternum, precluding volume measurement.

Results

Goiter

The prevalence rate of goiter or previous goiter surgery was high in Jutland (23 subjects had undergone thyroid operations, 19 for nontoxic goiter; and 12, nonoperated, had goiter), compared with Iceland (1 had undergone thyroid surgery for goiter and 1, in addition, had goiter). The difference was because of a high prevalence rate in females from Jutland (Fig. 2) [statistically significant in females ($P < 0.05$) with no difference in males]. In addition, there were few cases of treated hyperthyroidism and hypothyroidism (Jutland: 6 cases of previously treated hyperthyroidism, 6 patients receiving T_4 supplementation at the time of investigation; Iceland: none with hyperthyroidism and 1 receiving T_4).

TSH

Low TSH levels were common in Jutland (Fig. 3A), with 9.7% of values less than 0.40 mU/L [11 males, 31 females (5 of the females received T_4; 2 of the males and 5 of the

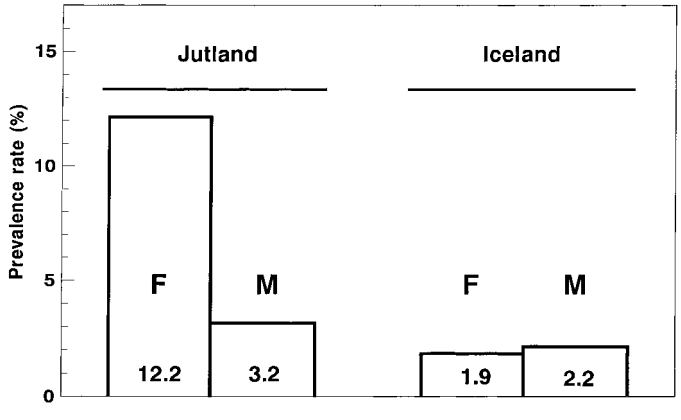

FIG. 2. Prevalence rate of goiter or previous goiter surgery in elderly females and males from Jutland and Iceland (significantly different in females, $P < 0.05$, with no difference in males.

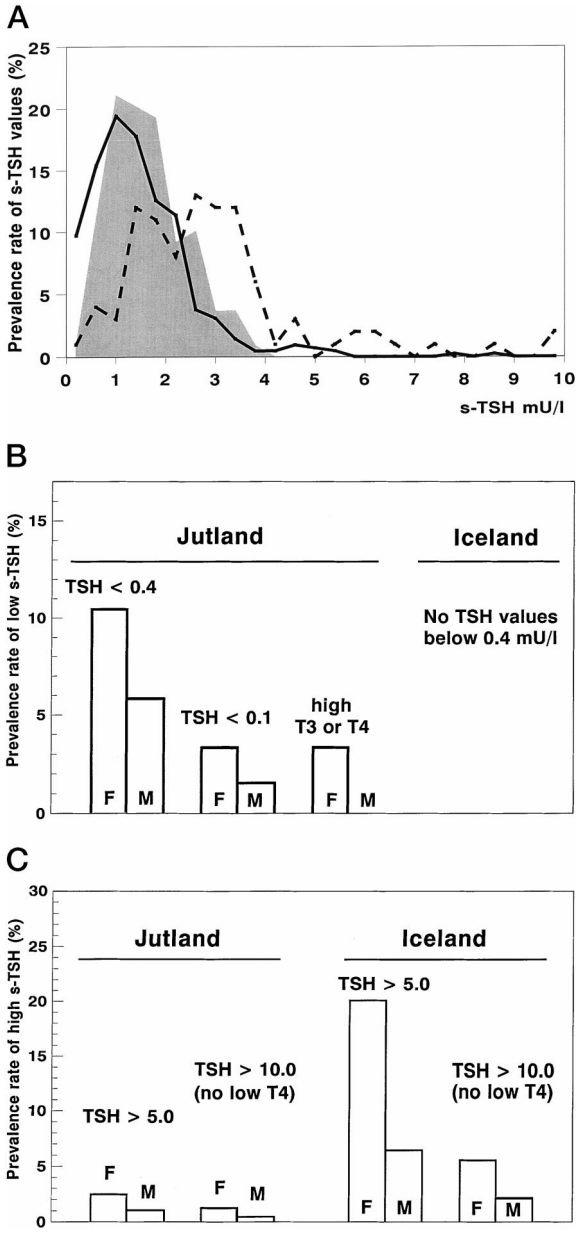

FIG. 3. A, Distribution of serum TSH values in elderly subjects from Jutland (*full line*) and Iceland (*dotted line*); intervals, 0.4 mU/L; values >10 mU/L: Jutland 0.9%, Iceland 4%. *Shaded area*, Serum TSH values in 109 normal healthy subjects from Jutland (51 M, 58 females, 20–40 yr old), measured as part of the characterization of the assay. B, Prevalence rate of thyroid hyperactivity, as evaluated by suppression of serum TSH and elevated serum T_4 and/or serum T_3. Subjects receiving T_4 were excluded. C, Prevalence rate of different degrees of impaired thyroid function, as evaluated by an increase in serum TSH.

females had goiter)], whereas this was seen only in one subject from Iceland (a male receiving T_4 supplementation). The distribution of TSH values in elderly subjects from Jutland was very similar to that of young subjects from this area, except for the high prevalence rate of values less than 0.4 mU/L in the elderly (Fig. 3A). The low serum TSH values were distributed over the range from <0.01 to 0.40 mU/L.

Thyroid hyperfunction

A low serum TSH in subjects not receiving T_4 may indicate thyroid hyperactivity or be caused by medication or severe nonthyroidal disease. None received medication suppressing serum TSH, except for T_4 substitution, and all were ambulatory without signs of severe disease. Figure 3B demonstrates the frequency of finding different grades of thyroid hyperactivity. This was very common in Jutland, especially in the females (females and males from Jutland compared with Iceland, and in Jutland females compared with males, $P < 0.01$, subjects receiving T_4 excluded). One of 30 of the elderly females from Jutland had unrecognized hyperthyroidism with suppressed serum TSH and elevated serum T_4 and or serum T_3.

Thyroid hypofunction

In Iceland, TSH values were not low; on the contrary, they were high, compared with values from Jutland (Fig. 3C) [Iceland: 18% had a TSH value >4.0 mU/L, this was 3.8% in Jutland ($P < 0.01$ in both males and females, and in both areas females *vs.* males)]. Some subjects had relatively high TSH values, more than 10 mU/L (4.0% in Iceland, 0.9% in Jutland), up to 50 mU/L, but none had a subnormal serum T_4. None of the subjects with high serum TSH had excessive amounts of iodine in urine, and none received medications with antithyroid action.

Thyroid Antibodies

All sera containing more than 10 mU/L TSH also had high concentrations of TPO-Ab and/or Tg-Ab. Antibodies were also common in subjects with normal serum TSH. The prevalence rates of detectable Tg-Ab and TPO-Ab were nearly similar (Fig. 4A), although many subjects had only one type measurable (89 subjects had TPO-Ab > 10 U/L, 50 of these had measurable Tg-Ab; 83 had Tg-Ab > 200 U/L, 44 of these had measurable TPO-Ab). Antibodies were nearly twice as common in females as in males ($P < 0.05$ in both areas). Both types of antibodies were approximately twice as common in Jutland as in Iceland ($P < 0.01$) (Fig. 4A).

Tg in serum

Serum Tg concentrations usually ranged between 5 and 15 μg/L in both populations (Fig. 4B). In Jutland, however, many values were much higher: among the females, 35.3% had Tg values above 30 μg/L, whereas this was seen in 20.5% of the males (Iceland females 6.3%, males 0%, $P < 0.01$ for both sexes).

Discussion

A comparative epidemiological study of elderly subjects was performed in Jutland, Denmark, with long-standing relatively low iodine intake and in Iceland with long-standing relatively high iodine intake. Abnormalities in thyroid function were common in both areas, with 13.5% of subjects from Jutland and 19% from Iceland having serum TSH values outside the reference range. However, in Jutland, values were predominantly low, indicating thyroid hyperactivity,

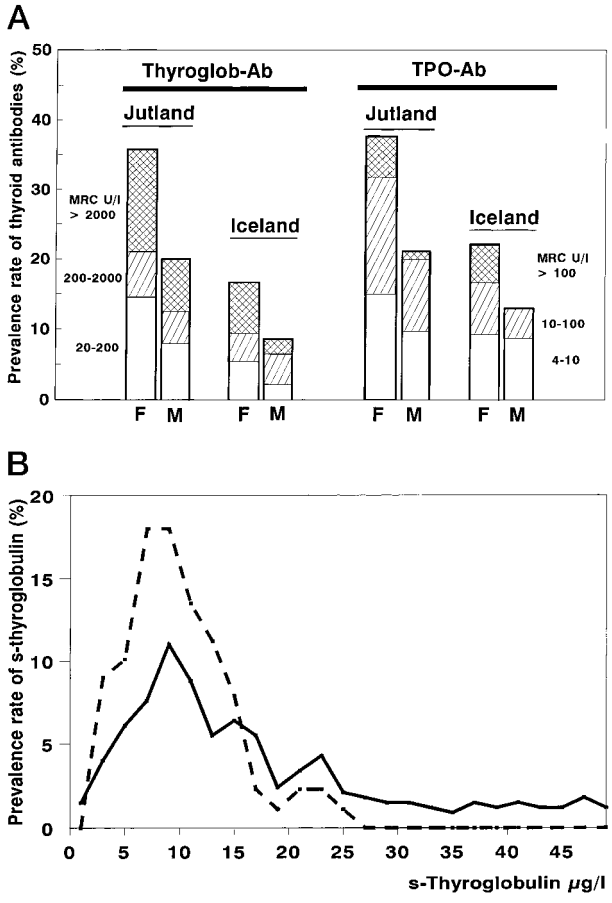

FIG. 4. A, Prevalence rate of Tg-Ab and TPO-Ab. Different levels are shown in each *bar*. B, Distribution of serum Tg values in elderly subjects from Jutland (*full line*) and Iceland (*dotted line*) (2-μg/L intervals). Only values from subjects who had not been treated for thyroid disease and subjects with Tg-Ab < 200 MRC U/L in serum were used for the calculation (Jutland males/females = 161/167, Iceland 42/47). In Jutland 14.2% of values were more than 50 μg/L (males: 10.6%, females: 18.6%); this was 3.4% in Iceland (males: 0%, females: 6.4%). Median values in Iceland were 9.5 μg/L (males: 8.6, females: 9.9), and in Jutland, 15.5 μg/L (males: 13.4, females: 18.6).

whereas in Iceland, high TSH values indicated impaired thyroid function.

In Jutland, the iodine intake has been stable (low) for many years, being in the order of 40–60 μg/day (12). Because studies of school children have shown no excessive goiter frequency (17), and newborns had normal thyroid function independent of iodine supplements (13), an iodine supplementation program has not been initiated. Apparently the group at risk at this low level of iodine intake is not children and young subjects but elderly females. In the present study, they had a high prevalence rate of clinical goiter and of various degrees of undiagnosed hyperthyroidism. In a previous comparative study, the incidence of diagnosed hyperthyroidism caused by multinodular toxic goiter was also excessive in this group (12). The dangers of such a condition are predominantly atrial fibrillation (18) (with a risk of impaired cardiac function and embolism) and osteoporosis (19).

In Iceland, several studies, over the years, have shown a high iodine intake (up to 300–350 μg/day) (10). Values from the present study were somewhat lower but still much higher than in Jutland. The change towards lower values could be caused by differences in eating habits between age groups or to changes, over time, in eating habits.

A major source of iodine intake in Iceland may be iodine in dairy products caused by feeding of cattle with fish meal. The iodine contents of two dairy milk samples from Reykjavik, measured as part of the current study, were 270 and 229 μg/L, whereas tap water contained less than 1 μg/L. Hence, an age-associated change from high intake of milk to water or coffee or to tea could be a reason for the iodine intake in elderly subjects in Iceland being lower than found in previous studies of young subjects. However, no special history on milk *vs.* coffee and tea intake was obtained in the subjects investigated. In Iceland, none had a low serum TSH (except for one subject receiving T_4). This corresponds to the very low incidence of diagnosed hyperthyroidism in elderly subjects from Iceland (12). On the other hand, subclinical hypothyroidism was very common (~4 times the prevalence rate in Jutland). The risks of such a condition may be an increase in lipid abnormalities with atherosclerosis and also in other abnormalities (20).

The high prevalence rate of subclinical hypothyroidism in Iceland could be caused by the high iodine intake. Iodine inhibits the thyroid (21), but when given to normal young subjects during short periods of time, the amount has to be considerably higher to induce an increase in serum TSH (22). Thyroids affected by autoimmunity are more sensitive to the inhibitory effect of iodine (23), and possibly, the subjects in Iceland with high TSH were those who, for other reasons, had autoimmune thyroiditis. Another possibility is that the high iodine intake in Iceland by itself worsens autoimmune thyroiditis in subjects who are genetically predisposed to develop thyroid autoimmunity. Such a mechanism is supported by series of animal experiments (24). Also, lymphocytic infiltrations of the thyroid in humans may be more common after an increase in iodine intake (25, 26). This relation between iodine intake level and autoimmune thyroid disease is in accordance with our previous finding that Graves' disease manifests at a considerably younger age in Iceland than in Jutland (12).

The comparative design of our study makes evident the difference between the areas with relatively low, and those with high, iodine intake levels. The results, however, are in line with those obtained in other epidemiological studies. In the United States, with relatively high iodine intake, the Framingham study showed that 4.4% of subjects 60–87 yr old had serum TSH more than 10 mU/L (27) (similar to the level found in Iceland). On the other hand, studies from European countries with relatively low iodine intake have shown a low prevalence rate of subclinical hypothyroidism and more hyperthyroidism, similar to Jutland [serum TSH >10 mU/L; Italy: 0.9% (28); Germany: 1.5% (29)]. Another example of the dominant effect of the iodine intake level on the type of thyroid disease is seen in patients receiving the iodine-containing drug, amiodarone. In the United States, the drug induced predominantly hypothyroidism; in Italy, hyperthyroidism (30).

All subjects, from both areas, with high serum TSH (>10 mU/L), had thyroid antibodies in serum; but in subjects with normal or low serum TSH, antibodies were more common in

Jutland than in Iceland. Hence, thyroid antibodies did correlate to impaired thyroid function, as evaluated by high serum TSH, but the population with the highest prevalence rate of antibodies was not characterized, in general, by high TSH levels. It had a high prevalence rate of goiter. A correlation between goiter and thyroid antibodies in serum has also been found in some other epidemiological studies. In the 20-yr follow-up study in Wickham, UK, subjects who had developed goiter had also developed thyroid antibodies (31). In Italy, Fenzi *et al.* (32) noted that thyroid antibodies were common in subjects with goiter and suggested that this was caused by long-standing goiter and that thyroid antibodies did not cause the goiter. Previously, thyroid antibodies and goiter were found to be more common in Scotland than in Iceland (33, 34).

A possible explanation for these findings is that TPO-Ab and Tg-Ab in serum are mainly markers and not inducers of disease and can result from different abnormalities. A common cause would be an autoimmune process in the thyroid (tending to inhibit thyroid function). This is the clinical pattern of autoimmune thyroiditis with circulation thyroid antibodies and impaired thyroid function (the insufficiency not being caused by the circulating antibodies but by the cellular autoimmunity in the gland). Antibodies might also be the result of goiter formation with exposure in the thyroid or release from the thyroid of antigens leading to autoantibody formation inside or outside the thyroid. Excessive Tg release from the thyroid was common in Jutland, and TPO may also be released from the thyroid (35). This is the clinical pattern of multinodular goiter with circulation thyroid antibodies but with no tendency to impair thyroid function. Formation of TPO-Ab and Tg-Ab may be induced easily in many subjects by one or another abnormality in the thyroid gland. This is not incompatible with the finding in animal studies of an enhancing effect of a high iodine diet on thyroid autoimmunity. The major event in this would be lymphocytic infiltration of the gland, and thyroid antibody formation would be a secondary phenomenon.

In conclusion, the study has demonstrated that both low and high iodine intake levels correlate to a high prevalence rate of thyroid abnormalities (although the types of abnormalities are different). It remains to be evaluated whether a window in iodine intake levels exists where thyroid disorders are less common. Probably mild iodine deficiency partly protects against autoimmune thyroid disease, as known from several animal strains (24). Knowledge of the iodine intake level of an area is valuable for the understanding of the pattern of thyroid abnormalities and for the planning of care of thyroid disorders.

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