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Increase in Incidence of Hyperthyroidism Predominantly Occurs in Young People after Iodine Fortification of Salt in Denmark

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Context: To prevent goiter and nodular hyperthyroidism, iodine fortification (IF) of salt was introduced in Denmark in 1998. We prospectively registered all new cases of overt hyperthyroidism in two areas of Denmark before and for the first 6 yr after iodine fortification.

Methods: We used a computer-based register of all new cases of hyperthyroidism in two population subcohorts with moderate iodine deficiency (Aalborg, n = 310,124) and mild iodine deficiency (Copenhagen, n = 225,707), respectively. Data were obtained 1) before IF (1997–1998); 2) during voluntary IF (1999–2000); 3) during the early (2001–2002) period of mandatory IF; and 4) during the late (2003–2004) period with mandatory IF.

Results: The overall incidence rate of hyperthyroidism increased [baseline, 102.8/100,000/year; voluntary IF, 122.8; early mandatory IF, 140.7; late mandatory IF, 138.7 (P for trend <0.001)]. Hyperthyroidism increased in both sexes ($P < 0.001$) and in all age groups: 0–19, 20–39, 40–59, and 60+ yr (P for trend <0.001). The increase was relatively highest in young adults aged 20–39 yr: late mandatory IF (percent increase from baseline), age 20–39, 160%, $P < 0.001$; age 40–59, 29%, $P < 0.01$; age 60+ yr, 13%, P = not significant.

Conclusion: Even a cautious iodization of salt results in an increase in the incidence rate of hyperthyroidism. Contrary to current concepts, many of the new cases were observed in young subjects, and are presumably of autoimmune origin. Furthermore, monitoring is expected to show a decrease in the number of elderly subjects suffering from nodular hyperthyroidism. **(*J Clin Endocrinol Metab* 91: 3830–3834, 2006)**

GLOBALLY, ABOUT one third of the world's population live in areas with risk of iodine deficiency (ID) and its complications (1–3). Iodine supplementation governed by national health care agencies and guided by international organizations (International Council for the Control of Iodine Deficiency Disorders, World Health Organization, and United Nations Children's Fund) has successfully eliminated or reduced the risk of ID disorders in most countries. Universal salt iodization is the main strategy, and currently about 70% of households worldwide have access to iodized salt (3).

When the iodine supply is low, the thyroid compensates by a number of mechanisms in an attempt to maintain sufficient thyroid hormone production (4). These compensatory mechanisms, over the years, may trigger development of multifocal autonomous growth and function of the thyroid gland with scattered cell clones harboring activating mutations of the TSH receptor (5, 6). As a consequence, mild and moderate ID is associated with a high incidence and prevalence of multinodular goiter and nodular hyperthyroidism, especially in middle-aged and elderly females (7, 8).

One of the main complications observed after initiation of iodine prophylaxis is iodine-induced hyperthyroidism (IIH), which has been reported in many iodine supplementation programs (9, 10). IIH seems to occur primarily in older subjects with autonomous thyroid nodules caused by longstanding low iodine intake. When the autonomous nodules are supplied with more substrate, as in iodine supplementation, the synthesis of thyroid hormones may exceed the physiological need, and a hyperthyroid condition develops. IIH may also occur in younger subjects whose autoimmune hyperthyroidism [Graves' disease (GD)] has not been expressed because of ID (10).

Iodine intake in Denmark was low for many years. In 1995, a working group of experts in nutrition and thyroid diseases recommended that the iodine intake in Denmark should be increased by introduction of iodized salt. This was among other things based on the finding of a mild to moderately low iodine intake and a high occurrence of nontoxic and toxic multinodular goiter in elderly subjects (8).

Voluntary iodine fortification (IF) of salt was introduced in Denmark in June 1998. The fortification was initiated cautiously with the permission of adding only 8 ppm iodine to all salt. In June 2000, this voluntary program was exchanged with a mandatory program of IF: household salt and salt for

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Abbreviations: GD, Graves' disease; ID, iodine deficiency; IF, iodine fortification; IIH, iodine-induced hyperthyroidism; ns, not significant; RR, rate ratio.

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commercial bread production should be iodized to 13 ppm. Both fortification levels were calculated to increase iodine intake by 50 μg/d, with more than 80% of the salt fortified. However, it was legal to use stores of unfortified salt. According to the Danish Food and Veterinary Research, these stores of salt were used in less than 1 yr.

In this prospective study, we registered all new cases of overt hyperthyroidism in two areas of Denmark with previously mild and moderate ID respectively. The register was started before and included the subsequent 6 yr after introduction of IF of salt. The investigation was part of the Danish Investigation on Iodine Intake and Thyroid Disease (DanThyr).

Subject and Methods

Population cohorts

Two open population cohorts representing the geographical variation in iodine intake in Denmark were selected for monitoring (11). As a representative of the moderately iodine-deficient Western part of Denmark, Aalborg and the surrounding municipalities in Northern Jutland were selected (n = 310,124). This area had moderate ID, with a median iodine concentration in urine of 45 μg/liter (12) (estimated iodine excretion of 62 μg/24 h) in subjects taking no mineral supplements. To represent the mildly iodine-deficient Eastern part of Denmark, the geographical area around Bispebjerg Hospital in Copenhagen was chosen (n = 225,707). This area had mild ID with a median iodine concentration in urine of 61 μg/liter (12) (estimated iodine excretion of 93 μg/24 h) in subjects taking no mineral supplements. If all subjects were included, the median iodine concentration in urine was moderately higher (Aalborg, 53 μg/liter; Copenhagen, 68 μg/liter).

The age and sex compositions of the two population cohorts were similar to the Danish population. Exact information on the cohorts was provided each year by the Danish Bureau of Statistics.

Identification of new cases of hyperthyroidism

Details on the register and the methodological evaluations performed before the registering was initiated have been described in detail previously (11). In brief, in Aalborg there was one laboratory and in Copenhagen there were three laboratories covering all of the respective cohort areas [the laboratory at Aalborg, Frederiksberg, and Bispebjerg Hospitals, and KPLL (the General Practitioners Laboratory in Copenhagen)]. Results from measurements of TSH and thyroid hormones were imported each week from the four laboratory databases into a register database. A filter was made to ensure that only results arising from general practitioner and hospital departments in the study areas were included. The database identified cases of overt hyperthyroidism according to the algorithm: low TSH (<0.2 mIU/liter) combined with high T_3 and/or T_4 in serum. The T_3 and T_4 results were evaluated with respect to the specific laboratory reference ranges (13). A list with possible new cases of hyperthyroidism was generated by the database. The list was manually evaluated by searching the laboratory and hospital databases, rechecking that the patient was living in the cohort area, and, furthermore, by contact to the patients' general practitioner. In Denmark, about 99% of the Danish population are registered with and consulting one general practitioner only. Cases previously identified by the register database were automatically excluded.

Laboratory activity

The database continuously accumulated information on the number of TSH and thyroid hormone measurements that had been performed in the two areas as part of diagnosis and control of thyroid disorders.

Statistical methods

Incidence rates were compared by a normal test with a continuity correction (14). Trend analyses were performed using the χ^2 test for trend (15). The 95% confidence intervals for rate ratios (RR) were calculated after log transformation of the respective rates (16). The calculations were based on an assumption of Poisson distribution of cases. Level of significance was set at 5%.

The study was approved by the regional Ethics Committees in Northern Jutland and Copenhagen.

Results

The investigation took place from 1997–2004 and comprised four periods: baseline (1997–1998), before IF was initiated, lasting 16 months in Aalborg and 14 months in Copenhagen. The following three periods lasted 2 yr each: 1999–2000, with IF on voluntary basis; 2001–2002, with early mandatory IF; and 2003–2004, with late mandatory IF. In the period with voluntary IF, the use of iodized salt and, thereby, the average increase in iodine intake was low (average, <10 μg/d). In the late mandatory IF period the increase in average iodine intake was calculated by the Danish Institute for Food and Veterinary Research to be about 60–65 μg/d. The calculations were primarily based on measurements of iodine content in bread and salt and knowledge of the Danes consumption of bread and salt.

At baseline, the crude incidence rate of hyperthyroidism in the entire Aalborg + Copenhagen cohort was 102.8/100,000/year. The incidence rate increased during voluntary IF to 122.8/100,000/year ($P < 0.001$) and further during early mandatory IF to 140.7/100,000/year ($P < 0.001$) before it became stable at a level about 35% above baseline.

The increase in occurrence of hyperthyroidism developed somewhat differently in the two subcohorts (Fig. 1), although it was statistically significant in both areas (P for trend <0.001). In Aalborg with moderate ID the increase in hyperthyroidism was more pronounced and evident before the increase in Copenhagen with mild ID.

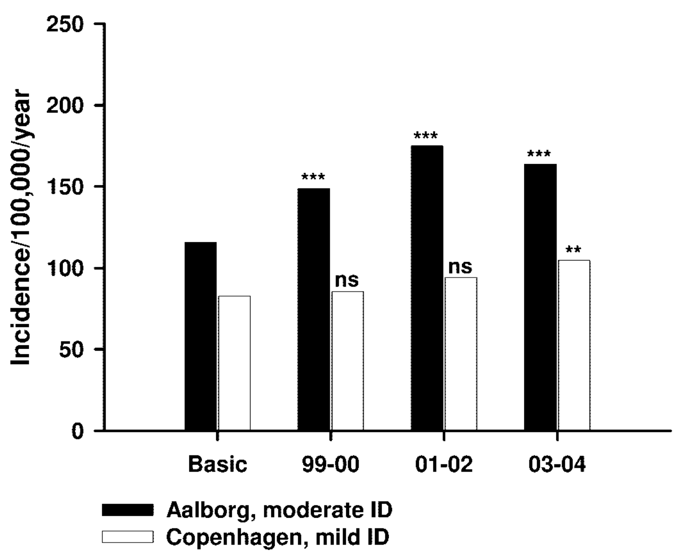

FIG. 1. The incidence rate of hyperthyroidism in Aalborg (moderate ID) and Copenhagen (mild ID) before and for the first 6 yr of IF of salt. Basic is the time before IF of salt (1997–1998), 1999–2000 is the period of voluntary IF, 2001–2002 is the early and 2003–2004 is the late period of mandatory IF. The incidence of hyperthyroidism increased significantly in both subcohorts during the study period. In Aalborg, the increase was more pronounced and before the increase in Copenhagen. Aalborg: baseline *vs.* voluntary IF, $P < 0.001$; voluntary IF *vs.* early mandatory IF, $P < 0.001$; early *vs.* late mandatory IF, ns. Copenhagen: baseline *vs.* voluntary IF, ns; voluntary IF *vs.* early mandatory IF, $P < 0.001$; early *vs.* late mandatory IF, ns. ⋆, Statistical significance compared with baseline (⋆, $P < 0.05$; ⋆⋆, $P < 0.01$; ⋆⋆⋆, $P < 0.001$).

As expected, hyperthyroidism was more common in females than in males ($P < 0.001$ in all four periods) (Fig. 2). A 35–40% increase in incidence rate of hyperthyroidism was observed in both sexes.

The age-specific incidence rates of hyperthyroidism (age 0–19, 20–39, 40–59, and 60+ yr) are shown in Fig. 3. In all age groups, there was a tendency toward an increase in hyperthyroidism during the study period (P for trend <0.001). However, when values from the baseline and late mandatory IF period were compared, the increase was only statistically significant in young adults and middle aged adults; baseline (1997–1998) *vs.* late mandatory IF (2003–2004), age 0–19 yr, P = not significant (ns); age 20–39, $P < 0.001$; age 40–59, $P < 0.01$; age 60+, P = ns.

In children and teenagers (age group 0–19 yr), the relative increase in hyperthyroidism was high with a RR at 2.8. However, due to the low incidence rate of hyperthyroidism in this age group, the total number of new cases was only 50. Twenty-nine (58%) of these were found in young adults aged 16–19 yr.

The relative changes (increase in percentage) in incidence of hyperthyroidism in adults are shown in Fig. 4. The highest relative and absolute increase was seen in the youngest age group (20–39 yr). In this group, hyperthyroidism increased about 160% compared with 29% in age group 40–59, and 13% in age group 60+ [RR (confidence interval): age 20–39, 2.61 (2.14–3.19); age 40–59, 1.29 (1.10–1.52); age 60+, 1.13 (1.0–1.28)].

The number of thyroid laboratory tests accumulated in the register database increased in both subcohorts during the study period (Table 1) (P for trend, Aalborg, $P < 0.001$; Copenhagen, $P < 0.001$) with minor differences between areas. During the baseline and voluntary IF period, more TSH per 100,000 inhabitants was analyzed in Copenhagen than in Aalborg, whereas the opposite relationship was present in the two periods with mandatory IF (Table 1).

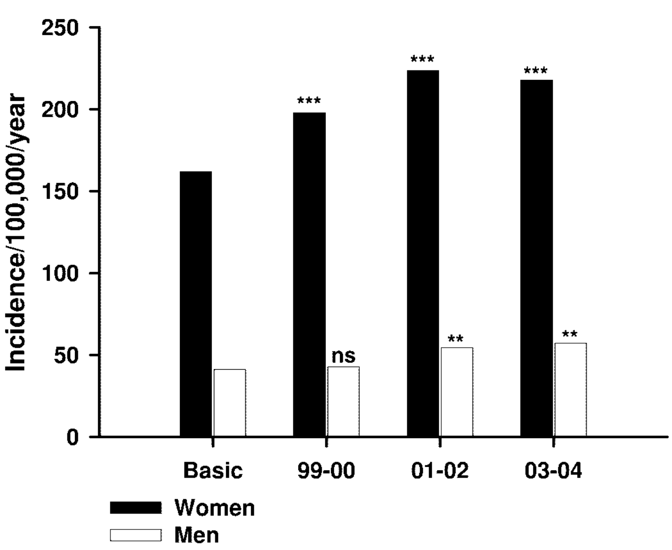

FIG. 2. The sex-specific incidence rate of hyperthyroidism in the combined cohort before (basic) and for the first 6 yr of IF of salt. The incidence rate increased in both females and males during the study period. In both sexes, the incidence rate became stable at the end of the study period at a level about 35% above baseline (female/male, 35 *vs.* 39%, P = ns). ⋆, Statistical significance compared with baseline (⋆, $P < 0.05$; ⋆⋆, $P < 0.01$; ⋆⋆⋆, $P < 0.001$).

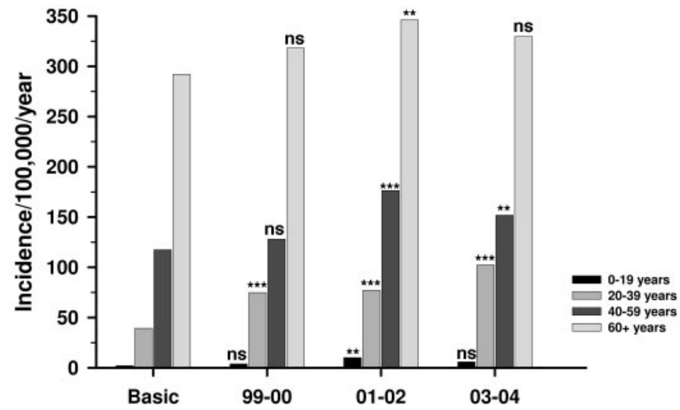

FIG. 3. The age-specific incidence rate of hyperthyroidism in the combined cohort before and for the first 6 yr of IF of salt. The incidence rate of hyperthyroidism increased significantly in all age groups during the study period (age 0–19, 20–39, 40–59, 60+ yr, P for trend <0.01 in all groups). In the late period with mandatory IF (2003–2004), the incidence rate of hyperthyroidism was significantly higher compared with baseline in the age groups 20–39 and 40–59 yr. ⋆, Statistical significance compared with baseline (⋆, $P < 0.05$; ⋆⋆, $P < 0.01$; ⋆⋆⋆, $P < 0.001$).

Discussion

In this prospective epidemiological study of a cohort representative of the Danish population performed before and during the first 6 yr of IF of salt in Denmark, we found that the incidence rate of hyperthyroidism increased significantly during the period with voluntary and early mandatory IF. At the end of the study period with mandatory IF, the incidence was stable about 35% above baseline. This increase in incidence of hyperthyroidism was present in each of two subcohorts with basically different iodine intake and in both females and males. Unexpectedly the most pronounced increase was observed in young adults aged 20–39 yr.

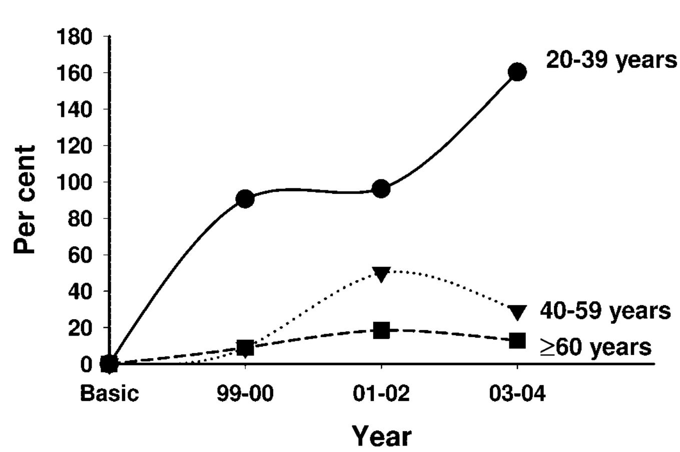

FIG. 4. The relative changes in age-specific incidence rates of hyperthyroidism (percent increase in incidence rate compared with baseline). Basic is the time before IF of salt (1997–1998), 1999–2000 is the period of voluntary IF, 2001–2002 is the early and 2003–2004 is the late period of mandatory IF. The age group 0–19 yr is not shown because the number of new cases of hyperthyroidism in this group was low. The highest increase was seen in age group 20–39 yr.

TABLE 1. Thyroid laboratory tests per 100,000 inhabitants per year from Aalborg (moderate ID) and Copenhagen (mild ID)

	Aalborg baseline	1999–2000	2001–2002	2003–2004	Copenhagen baseline	1999–2000	2001–2002	2003–2004	Total baseline	1999–2000	2001–2002	2003–2004
TSH	19,392	23,234	26,194	28,503	22,041	24,386	24,771	24,892	20,423	23,722	25,589	26,970
Total T_3	9,725	12,487	12,421	13,032	7,580	7,483	7,381	6,849	8,891	10,368	10,280	10,408
Total T_4	11,288	12,954	12,483	13,100	7,633	7,565	7,449	6,603	9,866	10,672	10,345	10,342
Free T_4[a]	0	0	0	0	2,718	2,953	2,822	3,933	1,043	1,251	1,199	1,669

Number of thyroid tests performed by the laboratories on subjects living in the two cohort areas.

[a] Many Danish laboratories are not using measurements of free T_4 and free T_3 in serum for routine due to the insufficient methodology of most commercial methods. In this study, free T_4 was only measured in two of the laboratories in Copenhagen.

Many studies have shown that iodine supplementation in an iodine-deficient population leads to an increase in the number of new cases of hyperthyroidism (17–22). In most studies, the finding has been based on patients referred to clinics and hospital departments and is not a result of systematic epidemiological surveys.

In Tasmania, IF of bread was introduced in 1963. The iodine content in bread became rather high and, as a consequence, the median 24-h urinary iodine excretion increased to a level of 173–264 μg/24 h. In a population of 371,000 subjects, the number of patients with overt hyperthyroidism referred to one of the two principal hospitals in the area increased from 65 to 218 yearly in 4 yr (17, 18). The increase in hyperthyroidism was seen mainly in subjects older than 40 yr of age. The epidemic of hyperthyroidism lasted 10–12 yr, and was followed by an incidence somewhat below that existing before the epidemic. In Switzerland, the iodine content of salt was increased in 1980 from 7.5 to 15 ppm giving an increase in median urinary iodine from 90 to 150 μg/g creatinine (19). During the first year, the number of patients with newly diagnosed overt hyperthyroidism referred to hospital increased about 27%, after which it gradually declined to 44% of baseline in 1988/89. The decline in hyperthyroidism was mainly due to a decrease in the incidence of multinodular toxic goiter, which declined 73%, whereas GD decreased 33% compared with baseline (19). In Austria, salt iodization was doubled in 1990 from 7.5 to 15.0 ppm. After 2 yr, a significant and clinically relevant increase in the incidence of both nodular toxic goiter and GD occurred as judged from the number of patients referred to Departments of Nuclear Medicine. The relatively highest increase occurred in the number of patients with GD. The high incidence persisted with GD being 73% above baseline, whereas nodular toxic goiter had decreased to near baseline after 5 yr. The increase in GD was evenly distributed among all age groups and both genders, whereas the increase in nodular toxic goiter was seen primarily in the elderly (20).

All the previous studies were based on patients referred to hospital departments. It is difficult to evaluate the quality of data based on referred patients as selection and change over time may occur when decision on referral is taken. Furthermore, the referral pattern may differ widely between countries and even regions.

In Iran, iodized salt was introduced in 1989. In a cross-sectional study of 6048 randomly selected subjects, the prevalence rate of overt hyperthyroidism was 0.34% 1 yr after 75% of the population had started using iodized salt. The authors concluded that no epidemic of hyperthyroidism had occurred (23). No data were available on the prevalence of hyperthyroidism before iodine supplementation.

The normal thyroid accommodates a moderate load of iodine through autoregulation (24). A nontoxic multinodular goiter with autonomous functioning nodules cannot do this, and extra iodine may lead to an increase in thyroid hormone production and IIH. Multinodular nontoxic goiter is common in populations with low iodine intake (25). The autonomous thyroid nodules presumably develop as a consequence of one or more of the processes involved in compensating for low iodide levels. A candidate process is generation of H_2O_2, which is up-regulated in thyroid follicular cells during ID (4).

IIH may also occur in patients with GD in remission after previous drug therapy (24) or in patients with subclinical GD. In some cases of IIH no underlying thyroid disease has been found (24). It may be speculated that insufficient autoregulation may develop after prolonged high activity caused by ID. Another possibility is that some of these patients had preexisting thyroid disease with focal areas of autonomy but clinically undetectable nodules.

Some studies indicate that IIH more often occurs in elderly subjects, whereas the disorder has been more or less evenly distributed throughout all age groups in other studies (9, 10). In the present study, the incidence of hyperthyroidism increased in all age groups; however, the increase was most pronounced, by far, in young adults.

The amount and duration of iodine supplementation is important for developing IIH. It has been shown that large amounts of iodine can cause IIH even after a very short period of time (26). On the other hand, it seems as if the thyroid is capable of handling small gradual increases in iodine intake (24), although IIH after iodine supplementation cannot be entirely avoided (27).

In the present study, we identified all cases of hyperthyroidism diagnosed as part of normal clinical activities. The diagnostic laboratories used sensitive assays for diagnosing thyroid diseases (11). Furthermore, we used a highly systematic approach with a computer-based system for identifying and registering of patients. All degrees of overt biochemical hyperthyroidism were identified in the cohort independent on whether the patient was seen in hospital, by a general practitioner or by a specialist in practice. It is possible that some cases of IIH are mild and, therefore, not referred to hospital. Such cases are obviously not registered in studies based on referred patients, and other types of bias may also have reduced the ability of previous studies to observe such a pattern.

A modest increase in the number of thyroid tests performed was observed over time. This may simply reflect the increased number of patients treated and controlled. However, it cannot be excluded that there has been an increase in the focus on diagnosing thyroid disease over time.

Currently, subclassification of new patients with hypothyroidism and hyperthyroidism identified before IF is under way (28), but we as yet have no data on the type of disease leading to hyperthyroidism in the present study. We previously found that GD was the dominant subtype of hyperthyroidism in young subjects (7), and it may be speculated that many of the new cases of hyperthyroidism observed after the increase in iodine intake suffered from GD. Animal as well as human studies have indicated that an increase in iodine intake may lead to more autoimmunity, at least in subjects with a certain predisposition (29–31). Further studies of the development of hyperthyroidism after IF are important to clarify this matter.

In conclusion, we found that even a cautious iodization of salt resulted in an increase in the incidence rate of hyperthyroidism. Contrary to current concepts, many of the new cases were observed in young subjects and were presumably of autoimmune origin. It is expected that the higher incidence of hyperthyroidism after IF is a transient phenomenon.

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