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An Increased Incidence of Overt Hypothyroidism after Iodine Fortification of Salt in Denmark: A Prospective Population Study

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Context: Iodine fortification (IF) of salt was introduced in Denmark in 1998. Little is known about the effect of a minor increase in iodine intake on the incidence of hypothyroidism. We prospectively identified all new cases of overt hypothyroidism in two areas of Denmark before and for the first 7 yr after IF had been introduced.

Methods: A computer-based register was used to identify continuously all new cases of overt hypothyroidism in two subcohorts with previous moderate and mild iodine deficiency (ID), respectively (Aalborg, n = 310,124, urinary iodine = 45 μg/liter; and Copenhagen, n = 225,707, urinary iodine = 61 μg/liter). Data were obtained 1) before IF (1997–1998), 2) during voluntary IF (1999–2000), 3) during early (2001–2002) and 4) during late (2003–2005) period with mandatory IF.

Results: The overall incidence rate of hypothyroidism increased during the study period: baseline, 38.3/100,000·yr; voluntary IF, 43.7 (not significant *vs.* baseline); early mandatory IF, 48.7 [*vs.* baseline, rate ratio (RR) = 1.27; 95% confidence interval (CI) = 1.10–1.47]; and late mandatory IF, 47.2 (*vs.* baseline, RR = 1.23; 95% CI = 1.07–1.42). There was a geographic difference because hypothyroidism increased only in the area with previous moderate ID: Aalborg, late mandatory IF *vs.* baseline, 40.3/29.7 (RR = 1.11; 95% CI = 1.11–1.66); Copenhagen, 56.7/51.6 (RR = 1.10; 95% CI = 0.90–1.34). The increase occurred in young and middle-aged adults.

Conclusion: Even a cautious iodization of salt was accompanied by a moderate increase in the incidence rate of overt hypothyroidism. This occurred primarily in young and middle-aged subjects with previous moderate ID. ***(J Clin Endocrinol Metab* 92: 3122–3127, 2007)**

GLOBALLY, ABOUT ONE THIRD of the world's population lives in areas with risk of iodine deficiency (ID) and its complications (1, 2). Iodine supplementation governed by national health care agencies has successfully eliminated or reduced the risk of ID in most countries. Universal salt iodization has been the main strategy, and currently about 70% of households worldwide have access to iodized salt (http://www.iccidd.org).

It is well documented and accepted that a low iodine intake is associated with a high risk of disease, including brain damage and endemic goiter if the ID is severe (1). It is also documented that a very high iodine intake is associated with endemic goiter and elevated serum TSH (3), indicating impaired thyroid function.

One of the main complications observed after initiation of iodine prophylaxis is iodine-induced hyperthyroidism, which has been reported in many iodine supplementation programs (4, 5). However, little is known about the effect of iodine supplementation to populations with mild to moderate ID on the incidence of overt hypothyroidism.

The iodine intake in Denmark was stable low for many years. The low iodine intake was associated with a high occurrence of nontoxic and toxic goiter in the elderly (6, 7) and signs of insufficient thyroid hormone production in pregnant women who showed increase in TSH in late pregnancy. 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. It was recommended that the iodine fortification (IF) should be cautious and be accompanied by a monitoring program to register the effects and counteract any side effects of the IF program.

Voluntary IF of salt was introduced in Denmark in June 1998. The fortification was initiated with only 8 ppm iodine that could be added to all salt, but after 2 yr, this turned out to be inefficient. In June 2000, IF of household salt and salt for commercial bread production became mandatory, and the iodine content in salt was increased to 13 ppm. Both fortification levels were calculated to increase iodine intake by around 50 μg/d with more than 80% of the salt fortified. It was, however, legal to use stores of unfortified salt.

In this prospective study, we registered all new cases of overt hypothyroidism in two areas of Denmark with previously mild and moderate ID, respectively. The register was started before and included the first 7 yr after introduction of IF of salt. The investigation was part of the Danish investigation of iodine intake and thyroid diseases (8).

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Abbreviations: CI, Confidence interval; ID, iodine deficiency; IF, iodine fortification; RR, rate ratio.

Subjects and Methods

The investigation took place from 1997–2005 and comprised four periods: 1) 1997–1998, baseline, was before IF was initiated and lasted 16 months in Aalborg and 14 months in Copenhagen; 2) 1999–2000 with IF on voluntary basis; 3) 2001–2002 with early mandatory IF; and finally 4) 2003–2005 with late mandatory IF. In the period with voluntary IF, the iodized salt was not used by the food industry and it covered only around 50% of household salt. Accordingly, the average increase in iodine intake was low (on average, <10 μg/d).

Population cohorts

Two open population cohorts representing the geographical variation in iodine intake in Denmark were selected for monitoring (9). 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). To represent the mildly iodine-deficient eastern part of Denmark, the geographical area around Bispebjerg Hospital in Copenhagen was chosen (n = 225,707). Exact information on the cohorts was provided each year by the Danish Bureau of Statistics. Over the time period of the study, the changes in the age and sex composition of cohorts were negligible.

Iodine intake of the population

The iodine intake of the population was estimated by two cross-sectional studies and by an investigation of iodine content in bread and salt.

The first cross-sectional study (C1) took place at baseline and comprised 4649 subjects (10). The study confirmed that Aalborg had moderate ID and Copenhagen mild ID with a median iodine concentration in urine of 45 μg/liter and 61 μg/liter, respectively, 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) (11).

The Danish Institute for Food and Veterinary Research investigated the iodine content in bread and salt sold in Danish stores in 2002 (last year of the early mandatory IF period). Using databases on food consumption in Denmark, it was calculated that the iodine intake had increased about 60–65 μg/d (12).

The second cross-sectional study (C2) took place in the late mandatory IF period (2004–2005) and comprised 3570 subjects (13). The median urinary iodine excretion had increased to 86 μg/liter (estimated 24-h urinary excretion, 129 μg) in Aalborg and 99 μg/liter (estimated 24-h urinary excretion, 149 μg) in Copenhagen [including subjects taking individual iodine supplementation, the figures were 93 μg/liter (140 μg/24 h) and 108 μg/liter (162 μg/24 h) respectively].

Identification of new cases of hypothyroidism

Details on the register and the methodological evaluations performed before the registering was initiated have been described in detail previously (9). In brief, in Aalborg, there was one and in Copenhagen three laboratories covering all of the respective cohort areas [the laboratory at Aalborg, Frederiksberg, and Bispebjerg Hospitals and the General Practitioners Laboratory in Copenhagen (KPLL)]. Results from measurements of TSH and T_4 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 practitioners and hospital departments in the study areas were included. The database identified cases of overt hypothyroidism according to the algorithm of high TSH (>5.0 mIU/liter) combined with a low T_4 in serum. The T_4 results were evaluated with respect to the specific laboratory reference ranges (14). A list with possible new cases of hypothyroidism was generated by the database. The list was manually evaluated by searching the laboratory and hospital databases, by rechecking that the patient was living in the cohort area, and furthermore by contact with the patients' general practitioner. 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 T_4 measurements that had been performed in the two areas as part of diagnosis and control of thyroid disorders.

Statistical methods

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

The study was approved by the regional Ethics Committees in Northern Jutland and Copenhagen and the Danish Data Protection Agency.

Results

At baseline, the crude incidence rate of hypothyroidism in the entire Aalborg and Copenhagen cohort was 38.3/100,000·yr. The incidence rate was stable during voluntary IF (*vs.* baseline, RR = 1.14; 95% CI = 0.98–1.33). During early mandatory IF, the incidence rate of hypothyroidism increased to 48.7/100,000·yr: early mandatory IF *vs.* baseline, RR = 1.27; 95% CI = 1.10–1.47. Afterward, it seemed to stagnate during late mandatory IF: late mandatory IF *vs.* baseline, RR = 1.23; 95% CI = 1.07–1.42 (Fig. 1).

Hypothyroidism was, as expected, more common in females than in males ($P < 0.001$ in all four periods). In females, the incidence rate of hypothyroidism increased about 20%

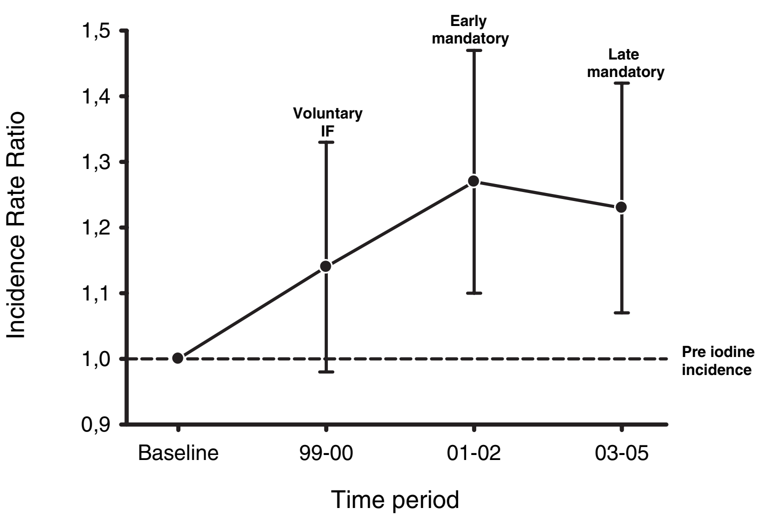

FIG. 1. The incidence RR of hypothyroidism in the total cohort (Aalborg and Copenhagen) in the three periods with different iodine fortification of salt *vs.* baseline, which is the preiodine incidence. The *vertical bars* indicate the 95% CI to the rate. In the period with voluntary IF, the incidence rate of hypothyroidism was equal to baseline because one was included in the CI. In the following two periods with mandatory IF, the incidence rate of hypothyroidism was significantly higher than baseline.

during the study period (incidence rate at baseline, 60.7/100,000·yr; late mandatory IF, 73.0; RR = 1.20; 95% CI = 1.03–1.41), whereas the increase in males was about 40% (incidence rate at baseline, 14.8/100,000·yr; late mandatory IF, 20.7; RR = 1.40; 95% CI = 1.02–1.92).

The response to increased iodine intake on the incidence rate of hypothyroidism was different in the two subcohorts. In Aalborg, with previous moderate ID, the incidence rate of hypothyroidism was 29.8/100,000·yr at baseline compared with 51.6/100,000·yr in Copenhagen with previous mild ID ($P < 0.05$). In Aalborg, the incidence rate of hypothyroidism was stable during voluntary IF (RR = 1.14; 95% CI = 0.91–1.42) but increased during mandatory IF (early mandatory IF *vs.* baseline, RR = 1.52, 95% CI = 1.23–1.88; late mandatory IF *vs.* baseline, RR = 1.35, 95% CI = 1.11–1.66). In Copenhagen, the incidence rate of hypothyroidism in all three periods with different IF was similar to baseline (Fig. 2).

In the combined cohort (Aalborg and Copenhagen), the incidence rate of hypothyroidism was stable in children and teenagers (age 0–19 yr) and in the elderly (age ≥ 60 yr) during the study period. However, in young adults (aged 20–39 yr) and middle-aged (aged 40–59 yr), the incidence rate of hypothyroidism increased significantly during mandatory IF (age group 20–39 yr, early mandatory IF *vs.* baseline, RR = 1.85, 95% CI = 1.22–2.79; late mandatory IF *vs.* baseline, RR = 1.90, 95% CI = 1.28–2.84; age group 40–59 yr, early mandatory *vs.* baseline, RR = 1.53, 95% CI = 1.12–2.10; late mandatory IF *vs.* baseline, RR = 1.81, 95% CI = 1.35–2.42). No obvious difference in pattern was observed between the Aalborg and Copenhagen subcohort (Fig. 3).

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 levels per 100,000 inhabitants were analyzed in Copenhagen than in Aalborg, whereas the opposite relationship was present in the two periods with mandatory IF (Table 1).

Discussion

In this prospective epidemiological study of a cohort representative of the Danish population performed before and during the first 7 yr of IF of salt in Denmark, we found that the overall incidence rate of hypothyroidism increased significantly during the period of mandatory IF. The increase was restricted to the subcohort with previous moderate ID, whereas the overall incidence of hypothyroidism was stable in the subcohort with previous mild ID. Unexpectedly, the increase in hypothyroidism was observed only in young adults and middle-aged (aged 20–59 yr).

It has been recommended that iodine supplementation should be followed by a monitoring program to register whether any side effects occurred. The focus has so far primarily been on iodine-induced hyperthyroidism (5, 17–19). However, several studies have shown that a high iodine intake may be associated with a higher prevalence of subclinical hypothyroidism in the population (7, 20, 21). This is the first study to study prospectively the effect of an increased iodine intake on the incidence of overt hypothyroidism.

It is difficult to compare results from different epidemiological studies on thyroid dysfunction because different biochemical and epidemiological methods have been applied and because the age and sex composition of the cohorts studied have differed. Genetic factors may in addition to environmental factors influence the results as well.

Small differences or changes in iodine intake may change the pattern of thyroid dysfunction. In the present study, there was only a slight difference in iodine intake between the two subcohorts. However, the incidence rate of hypothyroidism at baseline was significantly higher in Copenhagen (mild ID) than in Aalborg (moderate ID) caused by more cases of autoimmune hypothyroidism (22), whereas the opposite relationship was present for hyperthyroidism (14). This pattern with hyperthyroidism being more common than hypothyroidism has been confirmed in a number of epidemiological studies performed in areas with moderate and mild ID (7, 23, 24). On the contrary, studies from areas with sufficient or more than adequate iodine intake in general found a higher occurrence (prevalence or incidence) of hypothyroidism (subclinical or overt) compared with hyperthyroidism (7, 20, 21, 25–27).

In a 5-yr follow-up study in China including 3761 unselected subjects from three regions in China with mild, more

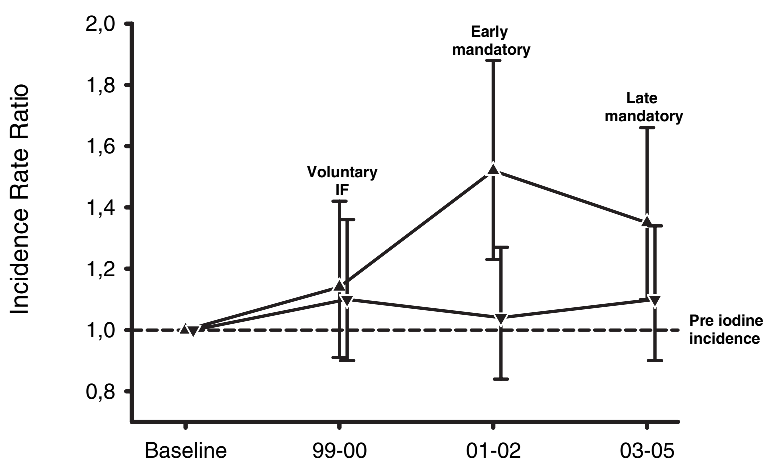

FIG. 2. The incidence RR of hypothyroidism in Aalborg (▲) with previous moderate ID and Copenhagen (▼) with previous mild ID in the three periods with different ID compared with baseline, which is the preiodine incidence. The *vertical bars* indicate the 95% CI to the rate. In Copenhagen, the incidence of hypothyroidism was stable. In Aalborg, however, the incidence rates of hypothyroidism were significantly higher in both periods with mandatory ID compared with baseline because one was not included in the 95% CI.

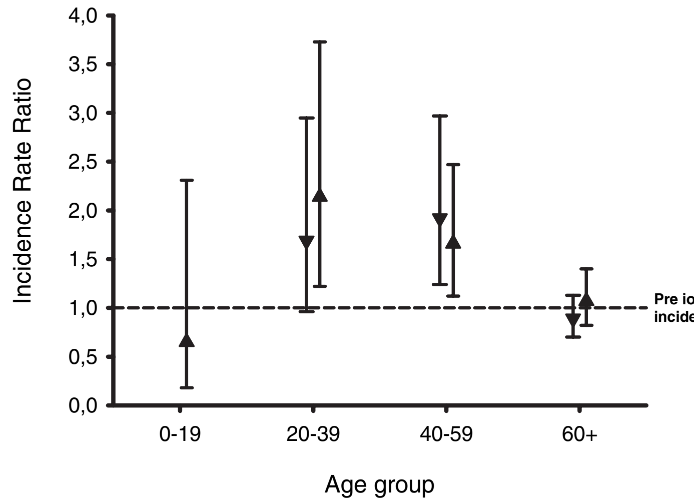

FIG. 3. The incidence RR of hypothyroidism in late mandatory IF period *vs.* baseline in children and teenagers, young adults, middle-aged, and elderly subjects above 59 yr. Results are shown for the Aalborg (▲) and the Copenhagen (▼) subcohort separately. Data from the combined cohort are given in the text. In Copenhagen, no cases of overt hypothyroidism were observed in the 0- to 19-yr age group at baseline, and the RR could not be calculated. The *dotted horizontal line* indicates the incidence at baseline. Values from late mandatory IF are significantly different from baseline when one is included in the 95% CI.

than adequate, and excessive iodine intake, the authors observed a high incidence of subclinical hypothyroidism and autoimmune thyroiditis with high iodine intake (20). There was no increase in overt hypothyroidism, which according to the authors might be related to the short follow-up time and long latency period for hypothyroidism. Moreover, the study cohorts were small for evaluation of overt hypothyroidism, and the number of observations may have been too low to detect an actual increase (type II error).

Despite the IF of salt in Denmark being introduced very cautiously, we registered an increase in the overall incidence of hypothyroidism when the iodine intake level was increased from moderate to mild ID. On the other hand, the overall incidence of hypothyroidism was stable when the iodine intake was increased from mild ID to a low recommended level of iodine intake.

The mechanism behind such an iodine-induced increase on the incidence of hypothyroidism is unknown. Several mechanisms may be involved, and the present results indicate that one or more mechanisms may operate already at a level of iodine intake low enough to give ID-associated disorders.

One possible mechanism could be the well known association between a high thyroidal iodine uptake and inhibition of many thyroidal processes probably via synthesis of iodine containing arachidonic acid derivates (28). It is well established that the autoregulation may be inappropriately high in a number of conditions including autoimmune thyroid disease, subclinical hypothyroidism, and previous surgery on the thyroid or treatment with radioiodine (29). Many of these conditions are rather common in the population (30, 31). This autoregulation of iodine metabolism within the thyroid gland was probably developed to protect against hyperfunction of the thyroid after a sudden iodine load (29). It could be speculated that the autoregulation might be less effective in elderly subjects compared with young adults and middle-aged.

Another possible mechanism behind iodine-induced hypothyroidism might be enhanced autoimmunity. Several animal studies (32, 33) and a study on lymphocyte infiltration in the human thyroid gland (34) have suggested that an increase from low to normal and high iodine intake is associated with a gradual increase in risk of autoimmune thyroid disease. A number of epidemiological studies in humans have not fully confirmed this association between thyroid autoimmunity and iodine intake. In a comparative study from Jutland (moderate ID) and Iceland (relative high iodine intake), Laurberg *et al.* (7) found the highest prevalence of both thyroid peroxidase and thyroglobulin antibodies in Jutland with the lowest iodine intake. In the United Kingdom, Prentice *et al.* (35), and in Sardinia, Loviselli *et al.* (36) found no relationship between previous and present iodine intake and the presence of thyroid autoantibodies in female blood donors and in schoolchildren, respectively. In a previous comparative cross-sectional study on the prevalence of thyroid autoantibodies we found a similar prevalence of thyroid peroxidase and thyroglobulin antibodies in Aalborg (moderate ID) and Copenhagen (mild ID) (30).

Finally, it could be speculated that a high or excessive iodine intake may lead to impaired thyroid function due to

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

	Aalborg				Copenhagen				Total			
	Baseline	1999–2000	2001–2002	2003–2005	Baseline	1999–2000	2001–2002	2003–2005	Baseline	1999–2000	2001–2002	2003–2005
TSH	19,392	23,234	26,194	28,737	22,041	24,386	24,771	25,208	20,423	23,722	25,589	27,239
TT_3	9,725	12,487	12,421	12,894	7,580	7,483	7,381	6,912	8,891	10,368	10,280	10,355
TT_4	11,288	12,954	12,483	12,951	7,633	7,565	7,449	6,642	9,866	10,672	10,345	10,273
FT_4[a]	0	0	0	0	2,718	2,953	2,822	3,946	1,043	1,251	1,199	1,675

Data are the number of thyroid tests performed by the laboratories on subjects living in the two cohorts areas. FT_4, Free T_4; TT_3, total T_3; TT_4, total T_4.

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

increased apoptosis of thyroid follicular cells as found in *in vitro* systems (37).

This study was a prospective follow-up study, and no control group with stable iodine intake was followed in parallel. It is therefore important to consider whether parts of the increase in incidence of hypothyroidism might be caused by other factors than the increased iodine intake. We previously found that the incidence of hyperthyroidism had increased in the years after IF of salt in Denmark (17). When we evaluated the diagnostic activity judged by the number of thyroid tests performed in the two subcohorts, we observed an increase over time. Clearly, some of this increase is linked to the increase in number of patients treated for hypo- and hyperthyroidism (17). However, from the data available, it cannot be excluded that part of the increase in incidence of hypothyroidism is caused by a higher diagnostic alertness.

In the present study, the follow-up time was 7 yr. It is possible that an even longer follow-up time is necessary to clarify the dynamics of the epidemiology of hypothyroidism after a sudden change in iodine intake.

In conclusion, we found that even a cautious iodization of salt resulted in a modest increase in the incidence rate of hypothyroidism. It occurred primarily in young and middle-aged subjects with previous moderate ID. Additional monitoring is necessary to observe the long-term effect of iodine fortification on hypothyroidism.

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