CLINICAL STUDY

Incidence of hyperthyroidism in Sweden

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Abstract

Introduction: The incidence of hyperthyroidism has been reported in various countries to be 23–93/100 000 inhabitants per year. This extended study has evaluated the incidence for ~40% of the Swedish population of 9 million inhabitants. Sweden is considered to be iodine sufficient country.

Methods: All patients including children, who were newly diagnosed with overt hyperthyroidism in the years 2003–2005, were prospectively registered in a multicenter study. The inclusion criteria are as follows: clinical symptoms and/or signs of hyperthyroidism with plasma TSH concentration below 0.2 mIU/l and increased plasma levels of free/total triiodothyronine and/or free/total thyroxine. Patients with relapse of hyperthyroidism or thyroiditis were not included. The diagnosis of Graves' disease (GD), toxic multinodular goiter (TMNG) and solitary toxic adenoma (STA), smoking, initial treatment, occurrence of thyroid-associated eye symptoms/signs, and demographic data were registered.

Results: A total of 2916 patients were diagnosed with *de novo* hyperthyroidism showing the total incidence of 27.6/100 000 inhabitants per year. The incidence of GD was 21.0/100 000 and toxic nodular goiter (TNG = STA + TMNG) occurred in 692 patients, corresponding to an annual incidence of 6.5/100 000. The incidence was higher in women compared with men (4.2:1). Seventy-five percent of the patients were diagnosed with GD, in whom thyroid-associated eye symptoms/signs occurred during diagnosis in every fifth patient. Geographical differences were observed.

Conclusion: The incidence of hyperthyroidism in Sweden is in a lower range compared with international reports. Seventy-five percent of patients with hyperthyroidism had GD and 20% of them had thyroid-associated eye symptoms/signs during diagnosis. The observed geographical differences require further studies.

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Introduction

Hyperthyroidism is a common condition with a wide variation in the reported incidence, reflecting various factors such as differences in dietary iodine intake, ethnical origin, and population structure. Hyperthyroidism is the most common cause of thyroid dysfunction in areas with mild and moderate iodine deficiency (1, 2). Worldwide previous studies have reported an incidence between 23 and 97/100 000 per year (1, 3–17). However, it is difficult to compare different studies due to the inclusion and exclusion criteria and the classification of subtypes of hyperthyroidism.

The most common form of hyperthyroidism is caused by increased thyroid hormone production in Graves' disease (GD), and the others are toxic multinodular goiter (TMNG) and solitary toxic adenoma (STA) (18). Hyperthyroidism is more common among women and affects around 2% of women and 0.2% of men (19, 20).

Previous studies in Sweden have reported an incidence between 25.8 and 43.0/100 000 inhabitants per year (4–6). Recently, we have reported the incidence for the Stockholm County to be 32.7/100 000 per year during the period 2003–2005. The incidence of GD was 24.5/100 000 per year, toxic nodular goiter (TNG) was 3.3/100 000 per year, and STA was 4.9/100 000

per year (15). The present group has also recently reported that the incidence of GD has increased and TMNG and STA decreased in the city of Malmö between 1988–1990 and 2003–2005 (16).

This study aims to estimate the incidence of hyperthyroidism nationwide and to identify the subgroups (GD, TMNG, and STA). We used a period of 3 years (2003–2005) to register all patients independent of age with *de novo* hyperthyroidism in a multicenter study covering ~40% of the Swedish population.

Materials and methods

Study population

Patients of all ages, who were diagnosed with overt *de novo* hyperthyroidism in the years 2003–2005, were prospectively registered in a Swedish Multicenter Study (participating cities: Malmö, Karlskrona, Göteborg, Örebro, Eskilstuna/Katrineholm, Stockholm, and Uppsala) organized by the 'Swedish Thyroid Study Group'. The total mean number of residents in these cities was 3 526 246 inhabitants, and in the whole of Sweden, there were 9 million inhabitants during the study period. Sweden is considered to be iodine sufficient with no geographically significant differences in glandular volume in a recent survey. We therefore consider the population in this study to be iodine sufficient (21, 22).

In Sweden, the treatment of hyperthyroidism is mainly decided and initiated by a specialist physician. The physicians, who were participating in the registration, were all specialists in Endocrinology, Oncology, Nuclear Medicine, or Surgery with special interest in thyroid diseases. All possible measures were taken to ensure that no patients were missed. The patients were identified as having symptoms and/or signs of hyperthyroidism, suppressed TSH (<0.2 mU/l), and elevated concentrations of more than one of the following thyroid hormones: total thyroxine (T_4), free T_4 , total triiodothyronine (T_3), and free T_3 . Autoimmunity was screened by measuring thyroid peroxidase antibodies and antibodies against the thyrotropin receptor (TRab) either by TRAK RIA provided by Brahms Diagnostica, Berlin, Germany (reference limit <8 U/l), or by Dynotest TRAK human provided by Brahms (reference limit <1.5 U/l) depending of the center involved.

Criteria of GD were as follows: laboratory-confirmed hyperthyroid patients with diffuse normal or enlarged thyroid gland, elevated Trab, and/or a verifying thyroid technetium scintigraphy that showed diffuse pattern of isotope uptake. For criteria of TNG (TMNG + STA), we used all patients with laboratory-confirmed hyperthyroidism and single or multinodular goiter and a concentration of TRab below detection limit for the assay. The TNG diagnosis was confirmed by scintigraphy showing an increased unifocal or multifocal isotope

uptake with suppression of normal thyroid tissue in the remaining parts of the gland. Exclusion criteria were as follows: subclinical hyperthyroidism, patients with a history or ongoing relapse of hyperthyroidism, destructive thyroiditis, or hyperthyroidism secondary to pharmacological treatment with amiodarone or interferon. As one inclusion criteria was a TSH value <0.2 mU/l, any patient with a TSH-secreting adenoma was not registered.

Data collection

Patients were registered only once and at the first visit when the diagnosis was confirmed at the participating centers.

Figure 1 (a) Incidence of hyperthyroidism in Sweden (GD, Graves' hyperthyroidism; TNG, toxic multinodular or uninodular goiter), *** $P < 0.0001$ compared with Sweden. (b) Incidence of Graves' disease in Sweden. (c) Toxic nodular goiter (TNG; toxic multinodular or uninodular goiter combined), *** $P < 0.0001$ compared with Sweden.

The following data were registered: age, sex, ethnic origin (country of birth), type of hyperthyroidism (GD and TNG), smoking habit, occurrence of thyroid-associated eye symptoms, and pretibial myxoedema. All eye symptoms, which were related to the hyperthyroid state (non-infiltrative) or the immune process (infiltrative) or thyroid-associated orbitopathy (TAO) in GD, were registered according to the clinicians' evaluation. A blood sample was drawn to evaluate the thyroid hormone levels and antibodies. A diagnostic thyroid scintigraphy and a 24 h ^{131}I uptake test were performed in selected cases. For each patient, the initially planned treatment was registered. We have specially concerned to ensure that all patients with thyrotoxicosis have been referred (which the guidelines for the primary care are clear about). We have sufficient confidence in the validation process of the registrations to judge whether the results correctly reflect the true incidence that we have obtained.

The study was approved by the Ethics Committee at Lund University: LU 790-02. All participating patients accepted the study after oral and written information was given.

Statistical analysis

The incidence rate was calculated by using the age- and sex-matched population. Fisher's exact test and logistic procedure with χ^2 test were performed. The Statistica 7.1, StatSoft, Inc., Tulsa OK, USA, was used for all computer analyses.

Results

Total incidence

In the 3-year period, 2916 patients with hyperthyroidism were diagnosed. The mean annual total incidence of hyperthyroidism in the total population was 27.6/100 000 inhabitants (Fig. 1a). The female to male ratio was 4.2:1 (Table 1). For females, the annual incidence was 44.1/100 000 and for males 11.0/100 000. The highest annual incidence of hyperthyroidism was 41.7/100 000 in the city of Malmö and the lowest was 23.1/100 000 in Göteborg ($P < 0.00001$). The incidence was higher in Malmö ($P = 0.0001$) and lower in Göteborg ($P = 0.0006$) compared with the Swedish population.

Hyperthyroidism: subgroup incidence

GD occurred in 2224 patients of the total population, corresponding to an annual incidence of 21.0/100 000 inhabitants. The highest incidence was found to be 29.6/100 000 in Malmö but was not statistically different from the average for Sweden ($P = 0.26$). The lowest incidence was found to be 16.7/100 000 in

Table 1 Subtypes of hyperthyroidism and gender ratio in Sweden.

Subtypes	Total <i>n</i> (%)	Female <i>n</i> (%)	Male <i>n</i> (%)	Female: male
Sweden	2916	2350	566	4.1:1
GD	2200 (75)	1754 (75)	446 (81)	3.9:1
TNG	684 (23)	577 (25)	107 (19)	5.3:1
Eskilstuna	139	110	29	3.7:1
GD	92 (66)	73 (66)	19 (66)	
TNG	47 (34)	37 (34)	10 (34)	
Göteborg	428	362	66	5.4:1
GD	367 (86)	309 (85)	58 (88)	
TNG	61 (14)	53 (15)	8 (12)	
Karlskrona	66	49	17	2.8:1
GD	52 (79)	39 (80)	13 (76)	
TNG	14 (21)	10 (20)	4 (24)	
Malmö	336	273	63	4.3:1
GD	239 (71)	189 (69)	50 (79)	
TNG	97 (29)	84 (31)	13 (21)	
Stockholm	1468	1166	302	3.8:1
GD	1097 (75)	849 (73)	248 (82)	
TNG	371 (25)	317 (27)	54 (18)	
Uppsala	267	220	47	4.6:1
GD	209 (78)	172 (78)	37 (79)	
TNG	58 (22)	48 (22)	10 (21)	
Örebro	172	143	29	4.9:1
GD	194 (81)	117 (82)	22 (76)	
TNG	33 (19)	26 (18)	7 (24)	

Eskilstuna (Fig. 1b). The female to male ratio was 3.9:1 (Table 1). The gender ratio was rather similar throughout the participating centers with the lowest seen in Karlskrona (2.9:1) and the highest in Göteborg (5.5:1).

TNG (STA and TMNG) occurred in 692 patients, corresponding to an annual incidence of 6.5/100 000. The highest annual incidence was 12/100 000 in Malmö and above the average for the study population ($P = 0.0001$). The lowest annual incidence was 3.3/100 000 in Göteborg and was below the average for the study population ($P = 0.0001$). The female to male ratio was 5.4:1 (Table 1).

Age-specific incidence

The majority of patients with GD were between 30 and 69 years of age and the majority of patients with TNG (TMNG and STA) were between 50 and 89 years of age. The highest age-specific incidence of GD was observed in the middle-aged patients; the peak incidence was observed in the group of 50- to 59-year-old patients (Fig. 2a). The highest incidence of TNG was observed in the group aged 70–79 years (Fig. 2b).

Thyroid-associated eye symptoms in GD patients

In the total population of patients with GD, 20.1% showed thyroid-associated eye symptoms of which 4.9% had infiltrative symptoms and/or signs (TAO) and 15.2% were non-infiltrative.

Figure 2 (a) Age-related incidence of Graves' disease in Sweden. (b) Age-related incidence/100 000 inhabitants per year of toxic multinodular and uninodular goiter in Sweden.

Smoking habit

Among the GD patients, smoking habit was reported in 1942 patients. Five hundred and forty-one (27.9%) of the patients were currently smoking, 482 (24.8%) of the patients had been a smoker, and 919 (47.3%) had never smoked. Among the TNG patients, smoking habit is found in 594 patients. One hundred and thirty-eight (23.2%) patients were currently smoking, 189 (31.8%) had been smoking, and 267 (44.9%) had never smoked. When non-infiltrative and infiltrative TAO was combined (Fig. 3), smoking was reported in 60% vs never smoking in 40%, not significantly different. Smoking habit did not seem to influence the presence of thyroid-associated eye symptoms in GD.

Seasonal specific incidence

The onset of hyperthyroidism was numerically highest in January in the GD (251) patients as well as in the TNG (78) patients. There were no statistically significant seasonal variations in the diagnosis of hyperthyroidism ($P = 0.59$).

Discussion

In this study, the total incidence of hyperthyroidism was 27.6/100 000 inhabitants per year in Sweden. The annual incidence of GD was 21.0 and of TNG was 6.5/100 000 inhabitants in the total population.

The total incidence is comparable to but in the lower range of previous international reports of 23–97/100 000 per year and considerably lower than a recent survey from another Nordic Country, Denmark (standardized incidence ratio (SIR) 81.6/100 000 per year) (3). The Danish study was performed from 1997

to 2000 in two regions with mild-to-moderate iodine deficiency. The design of that study was different from this study with a laboratory-monitoring system identifying subjects with pathological thyroid function tests. In addition, the Danish study included hyperthyroidism due to destructive thyroiditis, which was not included in this study. The large difference in the Danish study was in the incidence of TNG (SIR 39.8/100 000 inhabitants) compared with our results (6.5/100 000 inhabitants per year). This probably reflects that Denmark has had a historical lower iodine intake than Sweden. According to WHO and a recent survey of iodine intake, Sweden is sufficient (21). Differences in endemic iodine intake are very important for the occurrence of thyroid disorders (2). In areas with high-to-normal iodine intake (300 mg/day) such as Iceland, the incidences of new cases of GD are high compared with areas with low iodine intake (40–70 mg/day) such as Denmark (2). In addition, the iodine intake also influences the incidence of subtypes of hyperthyroidism as new cases of multinodular or uninodular goiter are more common in low-iodine areas (23). The incidence of GD was higher in Denmark (SIR 31.2/100 000 inhabitants) compared with Sweden (21.0/100 000 inhabitants per year) but rather similar to the incidence in Malmö (29.6/100 000 inhabitants per year).

This study corroborates earlier reports of the age-related incidence of GD and TNG where GD mostly occurred between 30 and 60 years whereas TNG occurred after 50 years of age (8, 10, 11, 15, 24, 25).

The total female to male ratio was 4.2:1, which is in accordance with previous studies that have shown 5.6 to 6.6:1 (4, 26). Of the subtypes, the sex ratio was highest for females with GD 3.9:1 as well for TNG 5.3:1.

In the total population of patients with GD, 20.1% showed thyroid-associated eye problems, when non-infiltrative and infiltrative symptoms/signs (TAO) were combined (Fig. 3). A positive correlation between smoking habit and occurrence of Graves' ophthalmopathy was found in 1987 and later confirmed in various surveys (27, 28). Smoking also increases the risk of development or worsening of TAO during medical or

Figure 3 Thyroid-associated eye problems in relation to smoking habit in Sweden.

radioiodine as we have recently reported from a prospective randomized study (29). Smoking habit, however, did not significantly influence the incidence of thyroid-associated eye problems or TAO in GD in this study. The reason is puzzling but it is not known whether the low frequency of smoking in Sweden did diminish or mask a likely association.

In this study, the highest number of patients with hyperthyroidism was registered in the month of January, although not statistically significant. This corroborates other studies showing the absence of seasonal variation (10) but is discordant with other reports of a higher frequency of hyperthyroidism in the spring and summer related to the iodine intake (30, 31) or increased temperature (32, 33). One could speculate whether infections might trigger the onset of hyperthyroidism in January. A theoretical association with the vitamin D level should also be considered as the 25-hydroxycholecalciferol concentrations decrease during late autumn to reach the lowest in January, which may influence the onset of hyperthyroidism (34, 35).

In this study, there were some geographical differences with the highest incidence of hyperthyroidism in Malmö, total incidence, and the incidence for GD and TNG. The reason for these differences is not apparent but might be related to ethnic differences, and a number of socioeconomic conditions, and demographic structure.

We have previously reported that between the years 1988–1990 and 2003–2005, the population in Malmö increased by 15% and the inhabitants born outside of Sweden increased by 54% (16). During the same time period, the incidence of GD in Malmö increased and the proportion of GD in immigrants was increased compared with patients born in Sweden (16). The proportion of TNG in patients born outside of Sweden was decreased compared with patients born in Sweden (16). We have no detailed information about these conditions in the other participating centers.

Taken together, these regional differences point toward disease-related causes rather than study design. Both Malmö and Göteborg have had comparatively large immigration during recent decades and ethnical and socioeconomic variations between the two cities may be of importance. Both GD and TNG show clear-cut age-related differences in incidence, and at present, it is not known to us whether there are important imbalances in age distribution in the background population between Malmö and Göteborg, which may influence on the incidence of hyperthyroidism and subtypes we have registered.

Göteborg is situated close to a salt-water sea and people of Göteborg have had a traditionally high dietary consumption of fish, which may be reflected by the low prevalence of goiter historically and presently (22). Longtime sufficient iodine intake therefore could be one of the many unknown reasons for the lower incidence of

TNG we found in Göteborg compared with the average for Sweden. Another contributing factor could be a different clinical handling in the Göteborg area if patients with subclinical hyperthyroidism due to TNG systematically and over a considerable number of years have been successfully treated and therefore do not proceed to overt hyperthyroidism and registration in this study.

We are planning a 5-year follow-up of this patient group, where the first chosen and final treatment will be analyzed and compared to other recommendations (36).

The GP is the first base for a patient with thyrotoxicosis in Sweden. According to the guidelines of primary care, all GPs refer patients with thyrotoxicosis to one of the participating centers. In such a survey, one drawback is if these guidelines are not adhered to by the GP, then they treat the patient without referring them. We have been concerned about this possibility at all the participating centers from the beginning of our study. Each center has addressed the issue by all means. As an example, we in Stockholm (1473 patients) sent an inquiring letter to all GPs immediately after the study to ensure that no patients were treated by the GP only and were not included in the study. We received a sufficiently large feedback from the GPs to conclude that the incidence figures are correct.

Conclusion

The incidence of hyperthyroidism in Sweden (27.6/100 000 inhabitants) is in the lower range compared with earlier international reports. Seventy-five percent of the patients with hyperthyroidism had GD and 20% of them had TAO during diagnosis. We have observed clear geographical differences between different regions in Sweden. Smoking habit did not significantly influence the presence of TAO in GD in this study.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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