CLINICAL STUDY

Hyperthyroidism and suicide: a retrospective cohort study in Sweden

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Abstract

Objectives: Mental symptoms and impaired quality of life commonly occur in patients treated for hyperthyroidism. Our aim was to determine whether a history of hyperthyroidism implies an increased risk of suicide.

Design: Historic cohort study of 43 633 patients treated with radioiodine or surgery for hyperthyroidism between 1950 and 2005. The majority of the radioiodine-treated patients came from Stockholm. Two comparison cohorts consisted of 44 921 patients registered with an operation for atoxic nodular goitre between 1965 and 2005, and 354 861 patients with a cholecystectomy between 1965 and 2001.

Methods: Subjects were followed from the date of diagnosis until death, emigration or end of follow-up. Information on outcome was obtained from population and health registers.

Results: The number of observed suicide deaths was 134 in the study cohort. A naive comparison with the age-, sex- and calendar period-matched general Swedish population yielded a moderately increased standardized mortality ratio (SMR), but stratifications revealed that the excess was mainly driven by women from Stockholm, whose baseline suicide risk was higher than for women in the rest of Sweden. Using the population rates from Stockholm, the SMR among Stockholm women with Graves' disease was 1.14 (95% confidence intervals (CI) 0.66–1.86) and toxic goitre 0.99 (95% CI 0.51–1.72). A direct comparison between the study cohort and the combined comparison cohorts, with multiple adjustments (including adjustment for residence in Stockholm), yielded a relative risk of suicide of 0.93 (0.68–1.26).

Conclusions: This study did not confirm an increased risk of suicide among patients treated for hyperthyroidism.

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Introduction

Hyperthyroidism is caused by excessive TH concentrations due to increased synthesis and secretion from the thyroid. It is a common disease and affects ~ 2% of women and 0.2% of men (1). A recent survey has shown an annual incidence of 32.7/100 000 adults in Stockholm county (2). Mental symptoms such as nervousness, anxiety, poor concentration and personality changes are prominent (3–7). Long-term neuropsychiatric symptoms following hyperthyroidism have been shown even in patients who have been successfully treated (8–10). Several studies have also shown that the quality of life in many patients is severely impaired at long-term follow-up (10–12). Patients with previous Graves' disease in

particular seem affected, since 32–56% still felt tired, 23–38% gloomy and sad, 15–32% reported that the disease still affected them socially and 16–37% felt that they were 'worn-out' even 14–21 years after treatment (12). Depressed patients seem to have altered TSH response to TRH, which has been suggested to be associated with the risk of suicide (13). In addition, THs may also interact with important mood modulating neurotransmitter systems like the serotonin system (14, 15).

In a previous study of Graves' disease (12), we observed that 7 patients out of 179 had died, 2 of whom had committed suicide. In the present study, we aimed to test the hypothesis that hyperthyroidism increases the risk of suicide using a nationwide population-based cohort.

Methods

The study cohort included 44 234 individuals diagnosed with hyperthyroidism between 1950 and 2005 in Sweden. It consisted of two approximately equally sized subcohorts – one with individuals who had been treated with ¹³¹I for hyperthyroidism in 1950–2000, of whom the majority were included after 1975 and consisted almost exclusively of patients from Stockholm (16) and one subcohort with patients identified in the Swedish inpatient registry as having undergone surgery for hyperthyroidism between 1965 and 2005. The two subcohorts included Graves' disease and toxic uni- or multinodular goitre, as well as patients who had toxic nodular goitre with Graves' disease. As a comparison cohort, we identified 45 655 patients with a record of surgically treated atoxic goitre in the Swedish inpatient register between 1965 and 2005 (atoxic goitre cohort). As a second comparison cohort, we identified 354 861 patients registered in the inpatient register as having undergone cholecystectomy between 1965 and 2001 (cholecystectomy cohort).

Using the national registration numbers (NRNs) assigned to all residents in Sweden shortly after birth or immigration as unique personal identifiers, we linked the cohorts to the registers of total population, migration and causes of death for correct censoring. We excluded 601 734 and 16 270 records in the study cohort, atoxic goitre cohort and cholecystectomy cohort respectively, due to erroneous NRNs or other inconsistencies revealed during the record linkages. Thus, the study cohort comprised 43 633 patients, the atoxic goitre cohort 44 921 patients and the cholecystectomy cohort 338 591 patients (Table 1). All cohort members were followed from the date of first hyperthyroidism diagnosis (or 1 January 1961 for the earlier first diagnosis due to unreliable death registry data before that date), atoxic goitre diagnosis or cholecystectomy until death, emigration or end of study

(31 December 2005 for the study cohorts and the atoxic goitre cohort; 31 December 2001 for the cholecystectomy cohort), whichever occurred first. Underlying and contributory causes of death among deceased individuals were obtained from the essentially complete causes of death register, in turn based on obligatory death certificates issued by physicians.

In order to estimate the relative risk (RR) of suicidal death among hyperthyroidism patients in our study cohort, relative to the age-, gender- and calendar period-matched general Swedish population, we calculated the standardized mortality ratio (SMR), which is the ratio of observed to expected numbers of deaths due to suicide in the study cohort. The expected number was calculated by multiplying the mortality rates for suicide in the general Swedish population (divided into strata of 5-year age groups, gender and 5-year calendar periods) by the stratum-specific person-time accrued in the cohort. We calculated 95% confidence intervals (CI) of the SMRs by assuming that the observed number of suicidal deaths followed a Poisson distribution. Stratified analyses were performed by gender, age at diagnosis, follow-up time from diagnosis, calendar period of follow-up and place of residence (Stockholm versus rest of Sweden). Since the hyperthyroidism is usually more severe, has a faster onset (month) and has an autoimmune background in Graves' disease compared with the clinically milder and slowly developing (years) toxic nodular goitre, separate analyses were performed for the two diseases. As it was suspected that an increased suicide rate could be an unspecific phenomenon linked to the hospitalization as such, we also did direct comparisons between the study cohort and the comparison cohorts using Poisson regression, restricting to the follow-up period from 1965 to 2001 (for the cholecystectomy cohort, the end of follow-up was 2001) and adjusting for sex, age, time of inclusion into the cohorts, follow-up time, treatment modality (surgery or non-surgical treatment), recorded hospitalizations

Table 1 Overview of the three cohorts.

	All hyperthyroid	Atoxic goitre	Cholecystectomy
Number of subjects	43 633	44 921	338 591
Women	36 743 (84%)	37 772 (84%)	227 654 (67%)
Men	6890 (16%)	7149 (16%)	110 937 (33%)
Mean age (s.d.)	51.3 (16.8)	50.5 (14.3)	52.8 (16.6)
Diagnosis			
Graves' disease	25 391 (58%)		
Toxic nodular goitre	16 331 (37%)		
Toxic nodular goitre with Graves' hyperthyroidism (mixed)	1911 (4%)		
Place of residence			
Stockholmers	14 591	5684	55 119
Non-stockholmers	29 042	39 237	383 472
Years at cohort entry	1950–2005	1965–2005	1965–2001
Follow-up time (Person-years)	703 126.14	746 390.25	4 647 275.53
Number of suicides	134	102	1002

for psychiatric diseases prior to inclusion into the cohort (albeit this information might have been incomplete due to left truncation) and place of residence (Stockholm versus rest of the country).

The study was approved by the local ethics committee of Karolinska Institutet.

Results

Mean age at entry was 51.3, 50.5 and 52.8 years in the study cohort, atoxic goitre and cholecystectomy comparison cohorts respectively (Table 1). Women were in the majority in all cohorts (84% in both thyroid cohorts and 67.2% in the cholecystectomy cohort). A diagnosis of Graves' disease had been given to 25 391 patients, 16 331 were classified as having toxic nodular goitre and 1911 were recorded with both toxic nodular goitre and Graves' disease. A total of 134 (30 male and 104 female) suicide deaths were identified in the study cohort versus 108 expected, corresponding to an overall SMR of 1.24 (95% CI 1.04–1.47; Fig. 1). The excess mortality due to suicide was confined to women (SMR = 1.41, 95% CI 1.16–1.71), whereas the point estimate of SMR among men was 0.86 (95% CI 0.58–1.23). Stratification into Graves' disease versus toxic nodular goitre revealed that the excess was essentially confined to Graves' disease (SMR 1.35, 95% CI 1.07–1.66), while the SMR for toxic nodular goitre was 1.06 (95% CI 0.77–1.43).

Since the suicide rates for women in Stockholm County differ from those for women in the rest of Sweden, and Stockholmers were overrepresented in our study cohort, we stratified the female part of the cohort into residents of Stockholm and residents of the rest of Sweden. Naively using the nationwide Swedish

population rates, Stockholm women with either main type of hyperthyroidism seemingly had substantial excesses of suicide (point estimates of SMRs associated with total hyperthyroidism, Graves' disease and toxic nodular goitre were 1.60, 1.56 and 1.47 respectively). We therefore recalculated SMRs for Stockholm and non-Stockholm women using suicide rates specific for Stockholm County and for all of Sweden respectively. This analysis had to be restricted to women who entered the cohort in 1975 or later due to unavailability of specific Stockholm rates before this year. Figure 1 reveals that the excess among Stockholm women in the study cohort virtually disappeared when we used the appropriate Stockholm population rates. The SMRs for Stockholm women with any hyperthyroidism, Graves' disease and toxic nodular goitre were 1.10 (95% CI 0.73–1.58), 1.14 (95% CI 0.66–1.86) and 0.99 (95% CI 0.51–1.72) respectively (Table 2).

Also non-Stockholm women with Graves' disease appeared to exhibit a sizeable excess when we analysed SMR using the national population rates. However, these women represented the oldest part of the radioiodine cohort, with hyperthyroidism diagnoses dating as far back as 1950. As this old cohort was not evenly distributed across non-Stockholm Sweden, we could not exclude bias through geographic mismatch between the observed suicide rate and the population rate (all of Sweden) used for comparison. Moreover, the validity of suicide diagnoses in the death register during the 1960s and early 1970s is less well documented. We therefore made a restriction to non-Stockholm women with Graves' disease who entered the cohort in 1975–2005. They were all identified in the Swedish inpatient register, which attained 75% coverage of the Swedish population in 1978. Then the SMR was 1.38 (95% CI 0.80–2.20).

Figure 1 Stratification of the standardized mortality ratios (SMR) and 95% confidence intervals (CI) of the study cohort.

Table 2 Poisson regression model to estimate the relative risk (RR) of suicide with confidence intervals (95% CI).

	RR (95% CI)
Disease ^a	
Hyperthyroidism	0.93 (0.68–1.26)
Cholecystectomy or atoxic nodular goitre	1.00 (Reference)
Follow-up time	
1 year	1.38 (1.10–1.73)
1–4 year	1.08 (0.92–1.26)
5–9 year	1.09 (0.93–1.27)
10+ year	1.00 (Reference)
Attained age	
> 75	1.32 (1.08–1.60)
65–74	0.97 (0.80–1.18)
55–64	0.97 (0.80–1.17)
45–54	1.13 (0.94–1.37)
00–44	1.00 (Reference)
Sex	
Men	2.73 (2.43–3.08)
Women	1.00 (Reference)
Residence area	
Other area	0.90 (0.77–1.05)
Stockholm county	1.00 (Reference)
Year of entry into cohorts (year of diagnosis or cholecystectomy)	
Before 1979	1.79 (1.47–2.18)
1980–1989	1.30 (1.06–1.59)
1990–	1.00 (Reference)
Treatment mode	
Non-surgery	1.19 (0.72–1.99)
Surgery	1.00 (Reference)
Psychiatric disease before entry to cohort	
Yes	7.39 (6.31–8.64)
No	1.00 (Reference)

^aAnalysis restricted to the follow-up period 1965–2001 (for the cholecystectomy cohort, the end of follow-up was 2001) and with mutual adjustments for all variables in the table.

In direct comparison between the study cohort and the combined comparison cohorts using Poisson regression with multiple adjustments, the RR among the former with the latter as reference was 0.93 (0.68–1.26).

Discussion

Among patients who had been treated with ¹³¹I or surgery for hyperthyroidism in Sweden from 1950 to 2005, we observed a moderately increased risk of death due to suicide, when naively using population rates from the entire Swedish population. Because the suicide rate in the general female population of Stockholm has been ~ 50% higher than the corresponding rate in the entire Swedish female population during the study period (17), the excess among Stockholm women essentially disappeared (RR for Graves' disease and toxic nodular goitre was 1.14 and 0.99 respectively) when we used the appropriated background rates. A direct comparison with hospitalized comparison cohorts (thyroidectomy for atoxic nodular goitre and cholecystectomy), which should have removed much of the possible unspecific effects of

the hospitalization or the treatment *per se* adjusting for a number of possible confounding factors including hospitalizations for psychiatric disease prior to inclusion, yielded a RR of 0.93.

Given the absence of any important elevations of suicide mortality in any other stratum (men, Stockholm women and toxic nodular goitre), the unexplained excess observed among non-Stockholm women with Graves' disease appears as an outlier result. Clearly, geographic mismatch between our cohort and the nationwide population rates explained some of this excess, which fell from 1.66 to 1.38 (non-significant) when we restricted our analysis to women included after 1974 (and thus improved – albeit not perfected – the geographic matching). Although we cannot exclude a true association, we interpret the remaining non-significant 38% excess as a chance finding.

Strengths of our study include the cohort design with practically all patients who received ¹³¹I treatment for hyperthyroidism in large parts of Sweden after 1950 and essentially all patients who were surgically treated for hyperthyroidism in Sweden after the mid 1980s.

Limitations to be highlighted include the absence of information about possible confounding factors, notably psychiatric status prior to diagnosis. Cross-linkage within the inpatient register made it possible for us to identify hospitalizations for psychiatric disease among some of our cohort members (at least after 1973 when the mental hospitals were connected to the registration), but due to left truncation and the unavailability of information about psychiatric outpatient care gives scope for residual confounding. However, negative confounding that has cancelled a true association seems unlikely. It should be noted that we did not adjust for psychiatric disease after onset of hyperthyroidism, because it could be in the causal chain to suicide. Moreover, we did not count suicide attempts because of the notorious difficulties with misclassification (17). If the case fatality among patients with suicide attempts would differ between our study and comparison cohorts, the comparison of suicide deaths may be a poor indicator of differences in the propensity to commit suicide. It should also be kept in mind that there is misclassification of fatal suicides, and a non-negligible proportion is classified as accidental deaths. Furthermore, although the number of patients in the cohort was large, the number of observed events was less impressive, at least in substrata, and our ability to detect small but clinically important excess risks was somewhat limited.

In conclusion, this study did not confirm our prior hypothesis of an increased risk suicide among patients with treated hyperthyroidism.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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