

A Literature Review on the Incidence of Autoimmune Thyroid Diseases

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Abstract

Background: Thyroid gland diseases are a public health problem worldwide. The epidemiology of autoimmune thyroid diseases was identified yet the pattern of autoimmune thyroid disorders incidence is unclear.

Methods: A review of the scientific literature from 1970 to 2016. Pubmed, Embase and CENTRAL were searched to identify randomized controlled trials that investigated the incidence of autoimmune Thyroid diseases as the primary endpoints. Identification of papers and data extraction were performed by two independent researchers.

Results: The reported incidence of autoimmune hypothyroidism varied between 2.2/100 000/year (males) and 498.4/100 000/year (females) and for autoimmune hyperthyroidism, incidence ranged from 0.70/100 000/year (Black males) to 99/100 000/year (Caucasian females). Higher incidence rates were found in women compared to men for all types of autoimmune thyroid disease. It is possible that non-autoimmune cases were included in the incidence rates reported here, which would give an overestimation in the incidence rates of autoimmune disease presented.

Conclusion: Studies of incidence of autoimmune thyroid disease have only been conducted in a small number. Our best estimates of the incidence of hypothyroidism is 350/100 000/year in women and 80/100 000/year in men; the incidence of hyperthyroidism is 80/100 000/year in women and 8/100 000/year in men.

Keywords: Thyroid Disease; Autoimmune; Hyperthyroidism; Hypothyroidism

Introduction

Autoimmune diseases are characterized by the activity of autoreactive lymphocytes, which cause tissue or organ damage through the formation of antibodies that react against host tissues, or effector T cells, which are specific for endogenous self-peptides [1]. Environmental and genetic factors cooperate in the induction of autoimmunity. Although several genes, including certain major histocompatibility complex (MHC) genotypes, are clearly associated with increased susceptibility to autoimmunity, monozygotic twins do not show complete concordance [2,3]. So, a disease-prone genetic background might not be sufficient for the clinical onset of autoimmunity.

Endocrine disease of the thyroid may result in either under- or overactivity of the gland and may be due to congenital factors, inadequate levels of dietary iodine intake, pregnancy, radiotherapy, viral infection, surgery, underlying disease such as infiltrative disorders, or

autoimmunity [4,5]. The incidence of thyroid disease caused by iatrogenic factors and iodine deficiency is clearly determined by environmental and clinical factors [6]. However, the pathogenesis of autoimmune thyroid disease is poorly understood although genetic factors are clearly important in both Graves' disease and autoimmune hypothyroidism [7]. Insight into the incidence of disease is important for the identification of trends in relation to patient characteristics such as sex and geographical location and to determine any changes in incidence following the introduction of new environmental factors.

Autoimmune thyroid disease (AITD) is a multifactorial or so-called 'complex' disease in which autoimmunity against thyroid antigens develops against a particular genetic background facilitated by exposure to environmental factors. AITD encompasses a spectrum of conditions ranging from Hashimoto's hypothyroidism (HH) at one end to Graves' hyperthyroidism (GH) at the other end. Thyroid peroxidase (TPO) and thyroglobulin (Tg) are the major autoantigens in Hashimoto's disease, but TPO-Ab and Tg-Ab occur also in w70% of patients with Graves' disease. The thyroid-stimulating hormone receptor (TSHR) is the major autoantigen in Graves' disease, but TSHR antibodies occur also in some patients with Hashimoto's disease. Graves' and Hashimoto's diseases share some but not all known AITD susceptibility genes. Similarly, for environmental exposures: one environmental factor may constitute a risk for both Graves' and Hashimoto's diseases or for just one of them, but another factor can be risky for Graves' disease but protective for Hashimoto's disease [8].

Methods

Scientific database search from 1970 to 2016

- Medline
- ScienceDirect
- EMBASE

Search terms: 'thyroiditis', 'thyroid autoimmune', 'Hashimoto' 'hypothyroidism', 'hyperthyroidism', 'Graves disease', 'epidemiology'.

Inclusion Criteria:

1. English language literature.
2. Cases checked to ensure that they were incident and not prevalent.
3. Etiology of thyroid disease was autoimmune and not secondary to another disease or environmental factors.
4. Review papers identified were searched for secondary references reporting on original research; secondary references found from any of the other papers reviewed were also included.

Exclusion Criteria: Prevalent cases or those thought not to be caused by autoimmunity will have led to overestimated.

Review papers identified were searched for secondary references reporting on original research; secondary references found from any of the other papers reviewed were also included.

Results

2339 publications were initially identified in the database, in addition to that, another 14 publications that were found through manual research. After removal of duplicates, abstracts and titles 1051 publications were assessed as identified from title and abstract, and 236 papers were excluded. 56 papers full text could not be retrieved and another 280 papers with the same cohort. There were also 459 papers excluded because they did not address autoimmune etiology causes or identified prevalence rather than incidence of Thyroid diseases. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results.

Finally 25 research and review studies were included and detailed as the focus for the present study Figure 1.

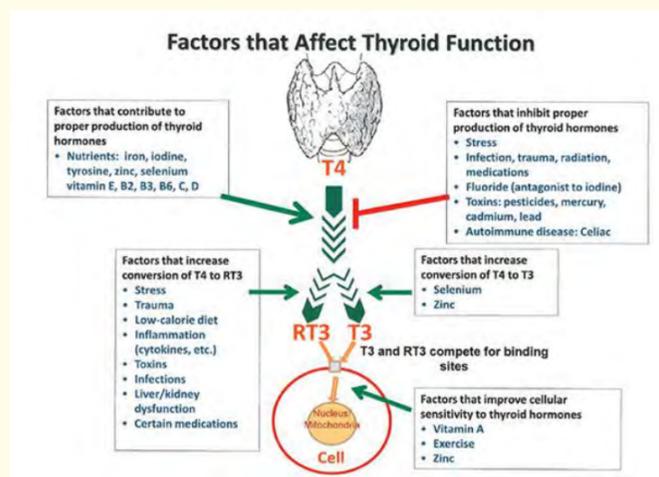


Figure 1: Factors impact thyroid function. *2011 The Institute for Functional Medicine

Hyperthyroidism

The incidence rates were summarized in Table 1. Rates were given for predominantly Caucasian populations; only one study [9] gave comparisons of incidence rates between different ethnic groups. They found that incidence rates in Asian and ‘coloured’ populations in Johannesburg, South Africa were slightly higher than Caucasian populations but incidence was lowest in the African population. Four studies reported on incidence in children and found, overall, that rates were between 0.1 and 5.0/100 000/year.

Study	Location	Period	Diagnostic test/criteria		Males	Females	Both
Hawazen A [26]	Makkah	2008	Iodine deficiency, and benign and malignant thyroid cancer revealed increase in males. Bad nutrition and goiter were increased in females				195
Nouh [27]	Libya	2008	Overt hyperthyroidism= 0.84%, subclinical hyperthyroidism = 0.84%				200
Sundbeck., et al.	Sweden	1971-1988	TSH. No separate identification of AI TD	70-81	100		
Galofre., et al.	Spain	1990-1992	Altered level of at least one of: TSH, FT4, TgAb and TMS Ab; positive TRAb. Identification of AI TD from Ab tests	All	2.1 (0.0-6.4)	41.9 (25.0-58.8)	24.2 (14.7-33.7)
Holm., et al.	USA	1989-2001	Defined as definite or probable.‡‡ No separate identification of AI TD	All		460††	
Houston., et al. [32]	USA	1954-1983	Diagnosed with hyperthyroidism and living in Rochester during study. No separate identification of AI TD	All			25.9
Flynn., et al.	Scotland	1993-1997	Received treatment for hyperthyroidism. No separate identification of AI TD	All	14.3 (11.4-17.2)	76.9 (70.3-83.5)	46.3 (42.7-49.9)
Leese., et al.	Scotland	1997	Received treatment for hyperthyroidism. No separate identification of AI TD	All	13 (9-20)	77 (65-90)	80 (60-140)
Vanderpump., et al.	UK	1972-1993	TSH; TgAb, TMS Ab and anti-thyroid cytoplasmic antibodies; FT4; thyroid size. Identification of AI TD from Ab tests	All			
Forssberg., et al.	Sweden,Västmanland ,Örebro, and Sörmland	1990-1999	TFT; TSH; FT4; clinical symptoms; immunological markers. Identification of AI TD from Ab tests	0-16	5.0	2.9	1.7
Wong and Cheng	China	1989-1998	Clinical features; size of thyroid; FT4; T3; TSH; TRAb from 1992. Identification of AI TD from Ab tests from 1992	0-14	0.9 (0.0-5.0)	9.5 (4.8-17.1)	5.0 (2.6-8.8)
Wong., et al.	China	1990-1994		0-14	0.8 (0.0-4.4)	7.2 (3.1-14.1)	3.8 (1.8-7.3)
Berglund., et al.	Sweden	1970-1974	Clinical symptoms; serum PBI; T3; presence/absence of TRAb; TRI uptake. Identification of AI TD from Ab tests	All	7.4	27.2	17.7
Brownlie and Wells	New Zealand	1983-1985	TSH; serum T4; FT4; serum T3; TMS Ab; Tg Ab. Identification of AI TD from Ab tests	All			23.5 (20.8-26.3)
Haraldsson., et al.	Iceland	1980-1982	RIA; T3; T4; free T4; resin T3; TRH response; T3 suppress; thyroid Ab tests; occasional thyroid scan. Identification of AI TD from Ab tests	All	8.9	38.4	23.6
Paunkovic., et al.	Serbia	1971-1990	Clinical, laboratory findings using RIA. Most had 131I and 99mTc thyroid uptake and thyroid scintiscanning. From 1986 TRAb tested for identification of AI TD	All			11.7‡
Kalk and Kalk	South Africa	1974-1984	Usual clinical criteria, elevated FT4, or by checking FT4 and T3 levels. Diffuse goitre confirmed by concentration of the isotope throughout gland. No separate identification of AI TD	African	0.70†	8.75†	
Barker and Phillips	England and Wales	1982	TFT. No separate identification of AI TD	All	9.2‡	35.5‡	22.7‡

Table 1: The incidence of Hyperthyroidism (crude rates/100 000/year unless stated otherwise).

A cross-sectional study conducted by Hawazen A (2016) [26] on the incidence of Thyroid disorders in Mekkah, Saudi Arabia iodine deficiency and benign and malignant thyroid cancer revealed increase in males while bad nutrition and goiter had higher rated in females.

The majority of studies based the diagnosis on both clinical criteria and biochemical tests of thyroid function [9-12]. Cases were identified for these studies either through sending questionnaires to relevant departments [10,12-15] or by checking hospital medical records or test result databases [9,11,16-18]. One study [20] used the Oakland Kaiser-Permanente Medical plan and free T4 index tests ordered by physicians to locate cases. One study did not give details about diagnostic criteria used [20] all of the studies looking at hypothyroidism also reported on hyperthyroidism, the details of which have been given above [21-23].

The incidence of overactive thyroid disease in Caucasian males ranged from 2.1/100 000/year in Spain [11] to 22.0/100 000/year [20] in Scotland, and in Caucasian females from 23.4/100 000/year in New Zealand [10] to 99/100 000/year in Scotland [23]. Sundbeck., *et al.* [21] found a slightly higher incidence rate in 70 – 81-year-old females but did not look at any other patient age groups. Where incidence rates were presented for males and females together, these ranged from 5.6/100 000/year in Serbia [18] to 52/100 000/year in Oakland, USA [19].

Comparing the incidence rates between different geographical locations within the countries reported on is difficult because only four studies gave rates by different locations [10,16,24] and none of these reported fundamental differences in incidence rates between the locations studied. Similarly, once study method had been taken into account, no large differences in incidence rates were observed between different countries. Where possible, only incidence rates of thyroid disease caused by autoimmunity were included; however, some studies did not give sufficient detail for this determination to be made and so nonautoimmune cases of thyroid disease may have been included in some of the rates.

Hypothyroidism

Incidence of hypothyroidism was summarize in Table 2 [22,23,24]. Common manifestation: rates were higher among women than men. All of these studies reported on the incidence of disease in predominantly Caucasian populations in Spain [11], Sweden [23] and the UK [21,23,25].

Study	Location	Period	Diagnostic test/criteria	Age (years)	Females	Males	Both
Hawazen A [26]	Makkah	2008	Psychic, congenital, diabetes, autoimmune thyroiditis (Hashimoto thyroiditis, Grave disease) and malignant thyroid were in males. Bad nutrition, iodine deficiency, goiter and benign thyroid cancer were increased in females.	All			196
Nouh [27]	Libya	2008	overt hypothyroidism = 1.12%, and subclinical hypothyroidism =6.18% thyroid dysfunction was more common in females higher prevalence of subclinical hypothyroidism 27%=subjects with hypercholesterolemia.	All			356
Sundbeck., <i>et al.</i>	Sweden	1971–1988	TSH. No separate identification of AI TD	70–81	200		
Galofre., <i>et al.</i>	Spain	1990–1992	Hypothyroid status, positive for TgAb or TMS Ab. Identification of AI TD from Ab tests	All	45.4 (28.0–62.9)	2.2 (0–6.5)	26.2 (16.3–36.1)
Vanderpump., <i>et al.</i>	UK	1972–1993	TSH; TgAb, TMS Ab and anti-thyroid cytoplasmic antibodies; FT4; thyroid size. Identification of AI TD from Ab tests	All	350 (280–450)‡	60 (30–120)‡§	
Flynn., <i>et al.</i>	Scotland	1993–1996	Long-term TRT. No separate identification of AI TD	All	498.4 (17.9–480.6)	87.6 (80.0–95.3)	297.5 (287.6–307.3)
Leese., <i>et al.</i>	Scotland	1997	Long-term TRT. No separate identification of AI TD	All	434 (406–463)	82 (70–96)	

Table 2: Hypothyroidism incidence by age and sex (crude rates/100 000/year unless stated otherwise).

One studies were conducted in the Arabian region , Saudi Arabia by Hawazen A [26] suggested evidence of manifestation of Hypothyroidism such as psychic, congenital, diabetes, autoimmune thyroiditis (Hashimoto thyroiditis) and malignant thyroid with higher rates in males while bad nutrition, iodine deficiency, goiter and benign thyroid was rather seen in females. On the other hand, another study by Nouh., *et al.* [27] has reported overt hypothyroidism of 1.12%, and subclinical hypothyroidism of 6.18% thyroid dysfunction was more common in females higher prevalence of subclinical hypothyroidism.

Three of the studies [11,21,25] examined hospital records using levels of TSH and thyroid hormone as indicators of hypothyroidism; Flynn., *et al.* [25] and Leese., *et al.* [23] identified cases of hypothyroidism from a prescription database (using prescriptions for anti-thyroid and thyroid replacement medication), a patient index, a thyroid register, morbidity records and a database with biochemistry data (using ICD-9 and ICD-10 codes). In the study by Vanderpump., *et al.* [21] patients were asked to complete a verbal questionnaire, thyroid size was graded and for those who had died, death certificates were checked as well as general practitioner (GP), hospital and postmortem records.

The rates presented by Vanderpump., *et al.* [21] Flynn., *et al.* [25] and Leese., *et al.* [23] for all ages compared well [21,25]. Sundbeck., *et al.* [22] reported incidence only in females aged 70 - 81 years whereas Galofre., *et al.* [11] reported the lowest rates, which are thought to underestimate the true incidence rates.

The above results concurred with systematic reviews conducted by McGrogan., *et al.* [28] and Shahrani AS., *et al* [29].

Discussion

Incidence rates of autoimmune hypothyroidism varied between 2.2/100 000/year and 498.4/100 000/year whereas incidence rates of autoimmune hyperthyroidism varied between 0.7/100 000/year and 99/100 000/year. Thyroid disease had a higher incidence in women.

In their review of the epidemiology of thyroid diseases, Tunbridge and Caldwell [30] point out that complications arise due to problems of definition, selection criteria and different techniques used for the measurement of thyroid function. In addition, symptoms of thyroid disease may be nonspecific or attributed to other diseases, which makes diagnosis more difficult [31].

When thyroid disease is caused by environmental factors, such as levels of iodine, incidence rates have been found to vary between locations and over time [32,33], Figure 2. For instance, in their study of the prevalence of thyroid disease in the elderly, Laurberg., *et al.* [34] found a high prevalence of hypothyroidism in Iceland, where the intake of iodine was high, but in Jutland, where iodine intake was low, a high prevalence of hyperthyroidism was found. In this review of autoimmune thyroid disease, the papers we identified came from a limited range of geographical areas. Consequently we could not comment on the absence or presence of differences in incidence rates between different geographical locations.

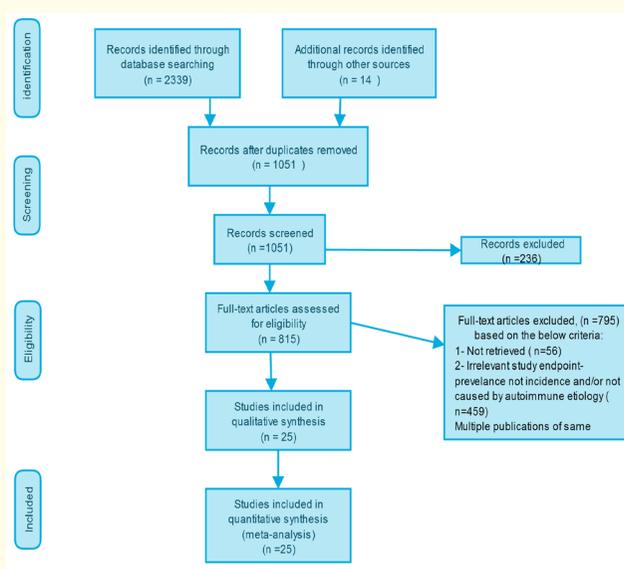


Figure 2: PRISMA chart illustrating the selection procedure of relevant articles.

There were over 100-fold differences in the incidence rates of various studies. Higher incidence rates tended to be due to the type of study conducted (e.g. where screening was used and therefore subclinical cases were included in the rates). The two prospective studies [21,22] produced the highest incidence rates of thyroid disease. One of these only included women aged 70 - 81 years [32]; the other used a multitude of data sources to evaluate and screen incident cases in the entire population and is the most comprehensive study we identified. The incidence rates of hypothyroidism in this study, which was carried out in the UK, were between 250 and 350/100 000/year (depending on the subgroup of the population). This was among the higher rates identified, partly as a result of the inclusion of subclinical cases. By contrast, a study carried out in Spain using a selected outpatients list reported an incidence rate in women of 45.4/100 000/year for hypothyroid disease; they will have missed any cases of thyroid disease who did not present at the participating outpatient clinic. In general, the incidence rates identified in the prospective studies will be more accurate. The difficulty with using these rates for post hoc evaluation of changes in incidence rates is that the prospective studies will have included subclinical cases.

Looking at the results for hyperthyroidism from retrospective studies, it is useful to note that the studies conducted in a similar way, through case finding from questionnaires, medical records or test results [10,24], produced similar incidence rates even though these studies covered different time periods between 1972 and 1999. This is an important finding as it indicates that, for autoimmune thyroid disease, the rates appear to be constant over time. However, a recent study from Scotland [23] found that the incidence of hyperthyroidism in females and hypothyroidism in males increased between 1997 and 2001. The authors note that this may be partly explained by an increase in the number of thyroid tests being carried out in the region, leading to an increased number of subclinical cases being identified. If this were a correct assumption then increases in the incidence rates for both types of thyroid disease and in both males and females would be expected unless there was differential testing between males and females. A true increase in incidence of thyroid disease caused by autoimmunity or some other cause cannot be ruled out but it is also possible that the increase seen was caused by an artefact. The studies included in this review mostly covered Caucasian populations, therefore we are unable to comment on potential differences in incidence rates between different ethnic groups.

In reviews covering the epidemiology of thyroid disorders, the distinction has been made between subclinical and overt hypothyroidism and hyperthyroidism [30]. However, in this review three studies that were conducted in a way that would include both subclinical and overt cases of hypothyroidism or hyperthyroidism: Vanderpump, *et al.* [21] and Sundbeck, *et al.* [22] and Nouh, *et al.* [27] examined all patients in their study cohorts for thyroid disease, which allowed them to detect subclinical cases of hypothyroidism and hyperthyroidism. All other studies used methods of case finding that did not involve the screening of patients. As Vanderpump, *et al.* pointed out, cases will be missed unless patients are screened for thyroid disease [21]; except for incidental findings subclinical disease will not, by definition, be readily detected clinically. In addition, the point where a patient is diagnosed and treated for thyroid disease, and when their disease becomes overt, differs widely in clinical practice and this will have resulted in differences in incidence rates between different geographical locations. However, given the combination of differences in rates and study design in different geographical locations, we cannot exclude the possibility that there is a geographical component to variations in incidence of thyroid disease.

Only two prospective and truly population-based studies [21,25] were identified. It could be argued that studies that were not population based or collected data retrospectively are more prone to producing under- or overestimated rates. For example, retrospective studies rely more heavily on physician or patient recall and will not necessarily identify all patients if records were destroyed, sent on to different hospitals, or otherwise lost for research purposes. These instances will have led to underestimated incidence rates. Inclusion of non-autoimmune disease (which may be more difficult to establish retrospectively) will have led to overestimated rates. Finally, retrospective assessment of population size or person-time contributed is often more difficult and therefore more prone to error than prospective collection of this information.

In an assessment of the incidence of autoimmune thyroid disease another important consideration is the likely cause of thyroid disease. Hypothyroidism may be caused by other factors including the exogenous causes of medication with lithium, radioiodine or anti-

thyroid drugs and thyroidectomy as well as the endogenous cause of autoimmune thyroiditis [36]. Similarly, in addition to autoimmune Graves' disease, hyperthyroidism may be caused by overzealous thyroid hormone replacement therapy, or by other endogenous thyroid disease including acute viral thyroiditis, toxic multinodular goitre or an autonomous adenoma. Rare causes include struma ovarii and pituitary hypersecretion of TSH. In this report, where possible, only incidence rates for autoimmune causes of thyroid disease have been included, although most papers did not specify in detail the causes of the thyroid disease reported. Associated with this issue is the possibility that euthyroid subjects with thyroid antibodies in the serum were included in incidence rates in those retrospective study designs that solely used results of biochemical tests for the diagnosis of thyroid disease. Therefore, it is possible that the rates presented overestimate the incidence of autoimmune thyroid disease.

There were highlighted difficulties in ensuring that all cases and only those cases of thyroid disease caused by autoimmunity, whether subclinical or overt, are included in the incidence rates. The most accurate incidence rates available come from prospective studies that screen patients. However, it is thought that retrospective case-finding procedures produce useful estimations of incidence rates providing the above limitations are taken into account.

Conclusion

From this comprehensive systematic review of autoimmune thyroid disease, our best estimate of incidence rates for hypothyroidism in females is 350/100 000/year and in males, 80/100 000/year; for hyperthyroidism in females 80/100 000/year and in males, 8/100 000/year.

Rates were generally higher among females: the incidence of hypothyroidism was between 2.2 and 111/100 000/year in males and between 200 and 498.4/100 000/year in females. For disorders of overactive thyroid disease, incidence rates for overt cases were between 0.7 and 22.0/100 000/year in males and between 8.8 and 46.5/100 000/year in females; studies including subclinical cases did not report incidence rates in males but reported higher incidence rates in females of around 80/100 000/year.

However, in view not only of the limited number of geographical areas covered but also the differences in methods used to determine incidence rates, caution is required in applying these figures to populations elsewhere in the world.

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