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Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease

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Summary

OBJECTIVE Autoimmune thyroid disease (AITD) is a common disorder especially in women, and both genetic and environmental factors are involved in its pathogenesis. We wanted to gain more insight into the contribution of various environmental factors. Therefore, we started a large prospective cohort study in subjects at risk of developing AITD, for example healthy female relatives of AITD patients. Here we report on their baseline characteristics.

SUBJECTS Only first- or second-degree female relatives of patients with documented AITD were included.

MEASUREMENTS Smoking habits, oestrogen use, pregnancy history and iodine exposure were assessed by questionnaires, and correlated to the thyroid function and antibody status.

RESULTS Of 803 subjects, 440 came from families with more than one patient with documented AITD. Of these families, 33% had documented cases of both Graves' disease and Hashimoto's thyroiditis. Although the subjects were in self-proclaimed good health, 3·6% were found to have hypothyroidism (overt disease in 1·3%) and 1·9% had hyperthyroidism (overt disease in 0·4%). These patients were older than the euthyroid subjects and were mostly positive for thyroid peroxidase (TPO) antibodies. Oestrogen use was associated with a lower rate of hyperthyroidism [relative risk (RR) 0·169; 95% confidence interval (CI) 0·06–0·52], whereas having been pregnant was associated with a higher relative risk for hyperthyroidism (RR 6·88; 95% CI 1·50–30·96). Of the 759 euthyroid subjects, 24% had TPO antibodies. Smoking and oestrogen use were negatively correlated with the presence of TPO antibodies. In the euthyroid subjects, TPO antibody titre correlated positively with TSH levels ($r = 0·386$; $P < 0·001$).

CONCLUSIONS The high prevalence of evidence for autoimmune thyroiditis at baseline supports the importance of genetic factors in its pathogenesis. The co-occurrence of Hashimoto's thyroiditis and Graves' disease within one family suggests a common genetic basis for these diseases. Oestrogen use is associated with a lower risk, and pregnancy with a higher risk for developing hyperthyroidism. The positive correlation between TPO antibody titres and TSH levels in euthyroid subjects suggests that TPO antibodies are indeed a marker of future thyroid failure.

Thyroid disease is common, especially in women (Canaris *et al*., 2000). The prevalence of hypothyroidism, both subclinical and overt, among adult females from all age groups ranges from 3·0 to 7·5% (Wang & Crapo, 1997). It is seen more frequently in elderly women. Parle *et al*. (1991) found an elevated TSH in 11·6% of 683 women above the age of 60 years, and roughly half of these women had evidence of thyroid autoimmunity. Hypothyroidism is more prevalent in areas of high iodine intake such as Iceland, with a prevalence of 18% in elderly women (Laurberg *et al*., 1998). The prevalence of hyperthyroidism in the general female population ranges from 0·9% (Konno *et al*., 1993) to 4·4% (Hollowell *et al*., 2002). It is more frequent in elderly women, and Parle *et al*. (1991) found a prevalence of 6·3%, although antithyroid antibodies were found in only 5·6% of these hyperthyroid females. The annual incidence of hypothyroidism in females has been estimated as 3·5/1000, while every year 0·8/1000 females will develop hyperthyroidism (Vanderpump *et al*., 1995).

The aetiology of autoimmune thyroid disease (AITD), encompassing Graves' hyperthyroidism and Hashimoto's thyroiditis, is multifactorial (Weetman & McGregor, 1994). Genetics play an important role in the development of AITD (Vaidya *et al*., 2002). The concordance rate for Graves' disease is much higher in monozygotic twins (35%) than in dizygotic twins (3%) (Brix

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et al., 2001) and the same applies to Hashimoto's hypothyroidism: 55% *vs.* 0% (Brix *et al*., 2000). In addition, many patients with AITD have family members also affected by this disorder. In a Hungarian study, 5·3% of patients with Graves' disease had a sibling with the same disorder (Stenszky *et al*., 1985). Using this and other studies, Vaidya *et al*. (2002) have estimated the λs for Graves' disease to be approximately 8. The inheritance of AITD is polygenetic and only a few of the susceptibility genes have so far been identified (Vaidya *et al*., 2002).

It has been estimated that 79% of the liability to develop AITD can be attributed to genetics (Brix *et al*., 2001) and therefore there are other environmental and hormonal risk factors involved (Weetman & McGregor, 1994). So far, the importance of these environmental and genetic factors has been studied taking them one at a time and not all together. Therefore, we decided to embark on a prospective cohort study in which we will follow for 5 years a large group of healthy females who are at increased risk of developing AITD because they come from families with at least one relative with documented AITD. Here we report on the baseline characteristics of this cohort.

Subjects and methods

We screened 1003 female subjects with at least one first- or second-degree relative with documented autoimmune hyper- or hypothyroidism, who were in self-proclaimed good health, without a history of thyroid disease, and between 18 and 65 years of age. The subjects were recruited through patients visiting our department, through advertisements in local newspapers and through thyroid patient self-support associations. After obtaining informed consent, we checked the medical history of the affected relative(s) regarding the autoimmune nature of their thyroid disease. Autoimmune thyroid disease was defined as documented hyper- or hypothyroidism in the presence of autoantibodies against thyroid peroxidase (TPO), TSH-receptor autoantibodies, histology compatible with autoimmune thyroiditis, or thyroid eye disease. In 200 of the 1003 screened subjects the autoimmune nature of the thyroid disease in their family could not be ascertained, leaving 803 participants to be included in the present study.

All subjects were seen at our Institution and after giving informed consent they were subjected to a brief medical examination and blood was drawn to assess thyroid status and to collect DNA. All subjects were asked to fill in questionnaires through which information was collected on smoking habits (current and past), use of oral contraceptives or other oestrogens (current and past), exposure to iodine excess, and the number of pregnancies. Current smoking was defined as smoking now, or having stopped smoking within 1 year of the study visit.

For this study, subclinical hyperthyroidism was defined as a TSH value of < 0·40 mU/l, whereas overt hyperthyroidism was diagnosed if the subject also had a free T4 (fT4) value of > 20·1 pmol/l, or a total T3 level of > 2·75 nmol/l. Subclinical hypothyroidism was defined as a TSH value of > 5·70 mU/l, overt hypothyroidism was diagnosed if there was also an fT4 level of < 9·3 pmol/l. These reference values were established in a different cohort of 75 women recruited from the general population by advertisement and in self-proclaimed good health and without a history of thyroid disease. These 75 women were between 20 and 69 years of age, and there were 15 females in each decade, resulting in a mean age of 42.

In all subjects fT4 (using time-resolved fluoroimmunoassay, Delfia, Turku, Finland) and TSH (Delfia) were measured, as well as antibodies against TPO and thyroglobulin (Tg) using a chemiluminescence immunoassay (LUMI-test, Brahms, Berlin, Germany). TPO and Tg antibody levels of > 100 kU/l were considered to be positive. TSH-receptor antibodies were measured by radioreceptor assay as TSH-binding inhibiting immunoglobulins (TBII, TRAK, Brahms, Berlin, Germany) and considered positive if > 12 U/l. Total T3 was measured by an in-house radioimmunoassay (RIA) in those subjects with a suppressed TSH level.

The study was approved by the local medical ethics committee.

Statistical analysis was carried out with the SPSS10 package, using unpaired Student *t*-tests or Mann–Whitney *U*-tests to compare means or medians. To compare rates among different groups, we used the χ^2-test or Fisher's exact test. Multiple logistic regression analysis was carried out to identify independent risk factors.

Results

Family history

The majority of our subjects (713; 89%) had at least one first-degree relative with documented AITD, whereas 90 (11%) had at least one second-degree relative with AITD. Four-hundred and forty subjects came from 233 families with more than one patient with documented AITD. In 47% of these families, only Graves' hyperthyroidism was found and in 20% all affected relatives had Hashimoto's hypothyroidism. However, in 33% both Graves' and Hashimoto's disease were diagnosed in the same family.

Prevalence of thyroid dysfunction

Of the 803 subjects seen at baseline and in self-proclaimed good health, 29 (3·6%) were found to be hypothyroid, 10 of whom had overt disease (1·3%). Of these 10, seven had permanent thyroid failure (all had high levels of TPO antibodies). Fifteen patients (1·9%) had hyperthyroidism, with three subjects having overt disease (0·4%). In only one of these latter three, Graves' hyperthyroidism was diagnosed with high TBII levels; the remaining patients had silent thyroiditis.

Table 1 Characteristics of 803 females with at least one relative with documented autoimmune thyroid disease, grouped for thyroid status at study entry

					P-value	
	All	Hypothyroid	Euthyroid	Hyperthyroid	Hypothyroid *vs.* euthyroid	Hyperthyroid *vs.* euthyroid
n	803	29 (3·6%)	759 (94·5%)	15 (1·9%)		
Age in years (mean ± SD)	36 ± 12	43 ± 12	36 ± 12	44 ± 10	0·003	0·02
TSH (median + interquartile range)	1·7 (1·2–2·5)	8·8 (7·6–11·8)	1·7 (1·2–2·4)	0·13 (0·0–0·33)	< 0·001	< 0·001
fT4 (median + interquartile range)	12·7 (11·3–14·3)	10·4 (8·5–11·9)	12·8 (11·5–14·4)	13·4 (11·2–16·2)	< 0·001	0·378
TPO-Ab > 100 kU/l	216 (27%)	25 (86%)	183 (24%)	8 (53%)	< 0·001	0·009
Tg-Ab > 100 kU/l	66 (8%)	7 (24%)	56 (7%)	3 (20%)	0·001	0·10*
TBII > 12 U/l	3 (1%)	0 (0%)	2 (0%)	1 (7%)	1·00*	0·06*
Smoking, ever	463 (58%)	20 (69%)	436 (57%)	7 (47%)	0·217	0·403
Smoking, current	280 (35%)	12 (42%)	266 (35%)	2 (13%)	0·484	0·101*
Oestrogen, ever	726 (90%)	28 (97%)	688 (81%)	10 (67%)	0·225	0·002
Oestrogen, current	360 (45%)	10 (34%)	348 (46%)	2 (13%)	0·225	0·016*
Pregnancy	415 (52%)	18 (62%)	384 (51%)	13 (87%)	0·279	0·006
Iodine intake excess	56 (7%)	1 (3%)	55 (7%)	0 (0%)	0·435*	0·279*

P-value for age was obtained by Student's *t*-test, *P*-values for TSH and fT4 were obtained by the Mann–Whitney *U*-test, *P*-values for the other variables by χ^2-tests or, if appropriate, by Fisher's exact test*. Hypothyroidism is defined as a TSH > 5·7 mU/l, hyperthyroidism as a TSH < 0·4 mU/l.

Table 2 Predictive value of some risk factors for the presence of hypothyroidism or hyperthyroidism in 803 females with at least one relative with documented autoimmune thyroid disease

	Odds ratio (95% CI)	
Determinant	Hypothyroid	Hyperthyroid
Age	**1·059 (1·027–1·093)**	1·006 (0·955–1·060)
Smoking, ever	1·299 (0·484–3·487)	0·892 (0·276–2·885)
Smoking, current	1·619 (0·731–3·583)	0·46 (0·10–2·12)
Oestrogen use, ever	4·232 (0·552–32 425)	**0·169 (0·055–0·523)**
Oestrogen use, current	0·889 (0·375–2·104)	0·356 (0·073–1·726)
Pregnancy	0·519 (0·197–1·368)	**6·88 (1·500–30·958)**
Iodine excess	0·332 (0·043–2·545)	–

Bold type, significant risk factors

Risk factors for thyroid dysfunction

The risk factors studied here are shown in Table 1. Patients with hypo- or hyperthyroidism were older than the euthyroid group. The strongest risk factor for both hyper- and hypothyroidism was the presence of TPO autoantibodies. Hyperthyroid subjects had a significantly lower exposure to exogenous oestrogens then the euthyroid subjects, and hyperthyroid subjects had been pregnant more often than the euthyroid subjects. Neither smoking history nor iodine excess in the previous year was found to be associated with dysthyroidism. Using multiple logistic regression analysis, having been pregnant was associated with an increased risk for hyperthyroidism, with an odds ratio (OR) of 6·88 [95% confidence interval (CI) 1·50–30·96], whereas exogenous oestrogen use was found to be associated with a decreased risk for hyperthyroidism (Table 2).

Risk factors for the presence of TPO antibodies

Although the majority of the hyper- and hypothyroid subjects had TPO antibodies, this marker for thyroid autoimmunity was also present in 24% of the euthyroid subjects (Table 3). When we looked at this latter group, the presence of TPO antibodies was associated with age and having been pregnant; the absence of TPO antibodies was associated with smoking and exogenous oestrogen use. Smoking habits and exogenous oestrogen use were both found to be independently associated with a reduced risk for TPO antibody positivity (Table 4).

TPO antibodies in relation to Tg antibodies and thyroid function

Twenty-seven per cent of the 803 subjects had TPO antibodies, whereas Tg antibodies were found in only 8% of the females. The large majority of the Tg antibody positive persons also had TPO antibodies; Tg antibodies as the only marker of AITD were found in only 3%. Interestingly, in the euthyroid subjects the TPO antibody titres were found to be correlated with increasing TSH levels, indicating the beginning of thyroid failure: Pearson correlation $r = 0{\cdot}386$, $P < 0{\cdot}001$ (Fig. 1).

Table 3 Age, hormonal status and risk factors in 759 euthyroid females with at least one relative with documented autoimmune thyroid disease, by TPO antibody status

	TPO-Ab = 100 kU/L	TPO-Ab < 100 kU/L	*P*-value
n	183 (24·1%)	576 (75·9%)	
Age in years (mean ± SD)	40 ± 12	34 ± 12	< 0·001
TSH (mU/L; median + interquartile range)	2·3 (1·5–3·3)	1·6 (1·1–2·2)	< 0·001
fT4 (pmol/L; median + interquartile range)	12·5 (11·2–13·8)	12·9 (11·6–14·5)	0·161
Smoking, ever	96 (52%)	340 (59%)	0·117
Smoking, current	46 (25%)	220 (38%)	0·001
Oestrogen use, ever	155 (85%)	535 (93%)	0·001
Oestrogen use, current	64 (35%)	284 (49%)	0·001
Pregnancy	106 (58%)	278 (48%)	0·023
Iodine intake excess	12 (7%)	43 (6%)	0·68

P-value for age was obtained by Student's *t*-test, *P*-values for TSH and f4 were obtained by the Mann–Whitney *U*-test, *P*-values for the other variables were obtained by the χ^2-test.

Table 4 Predictive value of some risk factors for the presence of TPO antibodies in 759 euthyroid females with at least one relative with documented autoimmune thyroid disease

Determinant	Odds ratio (95% CI)
Age	**1·037 (1·022–1·051)**
Smoking, ever	1·024 (0·681–1·540)
Smoking, current	**0·688 (0·480–0·986)**
Oestrogen use, ever	**0·578 (0·345–0·967)**
Oestrogen use, current	0·821 (0·565–1·193)
Pregnancy	0·726 (0·477–1·107)
Iodine excess	0·561 (0·287–1·096)

Bold type, significant risk factor

Discussion

This follow-up cohort study was initiated to determine risk factors involved in newly incident cases of AITD. To increase the likelihood of diagnosing new patients during a 5-year follow-up, we included subjects who had at least one relative with documented AITD and who were in self-proclaimed good health. Indeed, evidence for autoimmune thyroiditis was found in a fairly large proportion of subjects: 216/803 (27%) had TPO autoantibodies. In comparison, in the National Health and Nutrition Examination Survey (NHANES III), 14·6% of the females without known thyroid disease had TPO antibodies (Hollowell *et al*., 2002). In the first Whickham survey, 10·3% of the females had cytoplasmic antibodies (Tunbridge *et al*., 1977), and using a more sensitive assay a prevalence of 17·8% was found among female blood donors in the UK (Prentice *et al*., 1990). Our observed prevalence of 27% among first- and second-degree relatives of AITD patients thus lies between the prevalence in the general population and prevalence rates of 48% (Phillips *et al*., 1990a) and 43% (Prentice *et al*., 1990) in first-degree relatives. Our findings are thus in agreement with the notion that subjects with a family history of AITD are at increased risk for thyroid disease (Chopra *et al*., 1977; Carey *et al*., 1980; Tamai *et al*., 1990; Brix *et al*., 1998; Vaidya *et al*., 2002).

Even though the 803 participants were in self-proclaimed good health, 44 (5·5%) had an abnormal TSH value, of whom 29 (3·6%) had hypothyroidism (19 subclinical, 10 overt disease) and 15 (1·9%) were hyperthyroid (12 subclinical, three overt). Of the 759 participants with a normal thyroid function, 183 (24%) had TPO antibodies and in this group the presence of TPO antibodies correlated significantly with TSH levels ($r = 0·386$,

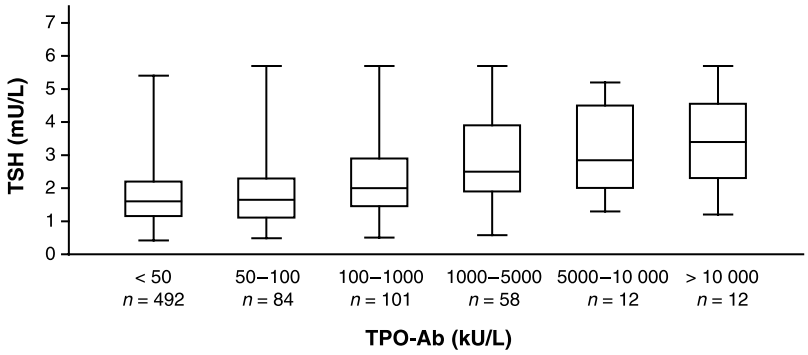

Fig. 1 Box and Whisker plots of TSH values grouped according to increasing TPO antibody (TPO-Ab) levels in 759 euthyroid relatives of patients with documented AITD, showing a positive correlation: Pearson correlation coefficient 0·386, $P < 0·001$.

$P < 0{\cdot}001$). This finding suggests that the presence of TPO antibodies is an early indicator of impending thyroid failure. This corroborates with studies showing that TPO antibody titres are related to the degree of lymphocytic infiltration of the thyroid gland (Yoshida *et al*., 1978).

All our subjects had a family history of at least one relative with documented AITD. As could be expected, 440 subjects (coming from 233 families) had more than one affected relative. Forty-six per cent of these 233 families had cases of hyperthyroidism alone, and 21% of hypothyroidism alone. Interestingly, in 34% of these families, patients with Graves' disease and Hashimoto's disease were found. This finding suggests that these two different types of AITD may have a common genetic background, because family members usually do not share environmental factors during their adult life but they do share some genes. We therefore suggest that environmental factors may dictate whether a subject with a certain genetic make-up will develop hypo- or hyperthyroidism, although, strictly speaking, the association might be the reverse.

Although delineating the relative importance of several environmental factors can be done more reliably in the future prospective follow-up of this cohort, the cross-sectional findings in our volunteers at study entry already provide some insight into some of these risk factors. First, both hyper- and hypothyroid subjects were older than their euthyroid counterparts, and second 86% of the hypothyroid cases had detectable levels of TPO antibodies. Interestingly, TPO antibodies were also present in 54% of the hyperthyroid patients.

Oestrogen use (current or past) was – independently from other factors – associated with a lower risk for hyperthyroidism, and was not associated with the occurrence of hypothyroidism. There are surprisingly few studies on the association between thyroid disease and oestrogen use. In one such study, current contraceptive use was found to protect against thyroid disease in general (thyrotoxicosis, myxoedema, or goitre) (Frank & Kay, 1978). These authors could not find a relationship between thyroid disease and parity, whereas we found that the hyperthyroid cases more often reported a pregnancy than the other two groups. It may be argued that subjects who have been pregnant are using oestrogens less often, but multiple logistic regression analysis showed that oestrogen use and pregnancy history were independently associated with hyperthyroidism, with a relative risk of 0·17 for oestrogen use and of 6·88 for pregnancy. In agreement with one other study, we could not find any association between parity and hypothyroidism (Phillips *et al*., 1990b).

Apart from TPO antibodies and age, we could not detect other factors increasing the risk for hypothyroidism. However, oestrogen use was associated with a lower rate of occurrence of TPO antibodies in the 759 euthyroid subjects (relative risk 0·58). Unexpectedly, we also found that smokers were less likely to have TPO antibodies than nonsmokers. Smoking is a risk factor for the development of Graves' hyperthyroidism (Prummel & Wiersinga, 1993) and it is difficult to understand why smoking would protect against the development of TPO antibodies. We can only speculate that the absence of TPO antibodies in subjects at risk of developing Graves' disease may increase the likelihood to become hyperthyroid. Only a prospective study will help to gain an insight into this.

There are obvious limitations of this study. Although our cohort will be followed prospectively, some of the current baseline findings are retrospective in nature, as exposure to certain risk factors was assessed retrospectively for the previous year. For example, iodine excess was assessed by history taking and this may explain why we could not find a relationship with the occurrence of hypo- or hyperthyroidism. Another important limitation is the fact that this is a selected group of subjects, from which we excluded relatives with known AITD. This means that certain established risk factors will not be detected in this first cross-sectional analysis because they will already have precipitated thyroid disease in some relatives. Such risk factors might become apparent in a future prospective analysis.

Despite these limitations, our study strongly supports the importance of genetic factors in the development of autoimmune thyroid disease in view of the high prevalence at baseline of autoimmune thyroiditis in this large group of subjects with a positive family history. Regarding this family history, it was striking to note that indeed both Graves' and Hashimoto's disease can occur in the same family. Our study also supports the importance of thyroid peroxidase antibodies as a marker for future thyroid failure in view of the positive correlation between TSH values and thyroid peroxidase antibody titres in the euthyroid subjects.

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