Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study

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Abstract

Objective: To evaluate the progression in time from euthyroidism to overt autoimmune hypothyroidism or to overt autoimmune hyperthyroidism.

Subjects and methods: The design is that of a nested case–control study within the prospective Amsterdam autoimmune thyroid disease (AITD) cohort study in which 790 healthy euthyroid women with at least one first or second degree relative with documented AITD were followed for 5 years. Thyroid function tests were assessed annually. Contrast between cases (overt hypothyroidism – TSH > 5.7 mU/l and free thyroxine (FT4) < 9.3 pmol/l and overt hyperthyroidism – TSH < 0.4 mU/l and FT4 > 20.1 pmol/l, also referred to as events) and controls (matched for age and duration of follow-up).

Results: At baseline, the 38 hypothyroid cases had already higher TSH and lower FT4 concentrations than their 76 controls, and the difference between both the groups persisted 1 year before occurrence of the event. In contrast, neither TSH nor FT4 values differed between the 13 hyperthyroid cases and their 26 controls at baseline or 1 year before the event. The prevalence of thyroid peroxidase-Ab was higher in both hypothyroid and hyperthyroid cases than in controls. At the time of event, hypothyroid cases were less common among current smokers (P=0.083) and more common in the postpartum period (P=0.006) than their controls, whereas hyperthyroid cases were pregnant more frequently (P=0.063).

Conclusions: The data suggest that progression toward overt autoimmune hypothyroidism is a gradual process taking several years, but in contrast overt autoimmune hyperthyroidism develops faster in terms of months.

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Introduction

In the perception of most clinical endocrinologists, the progression from euthyroidism to overt autoimmune hypothyroidism (Hashimoto’s thyroiditis) over time is supposed to be slow and insidious. On the other hand, the progression from euthyroidism to overt autoimmune hyperthyroidism (Graves’ disease) is believed to occur more rapidly, as symptoms in newly diagnosed Graves’ hyperthyroid patients have been present for a relatively short period of time.

Although to date many studies have investigated the progression rate from subclinical to overt autoimmune hypothyroidism or hyperthyroidism (1–13), a careful review of the literature however did not detect studies on the progression from euthyroidism to overt autoimmune hypothyroidism or to overt hyperthyroidism and with these premises we sought to assess the time course from euthyroidism to overt thyroid failure and the supposedly rapid progression from euthyroidism to overt thyroid hyperfunction.

Subjects and methods

Subjects

The original Amsterdam autoimmune thyroid disease (AITD) cohort consisted of 803 female subjects between 18 and 65 years of age, without a history of thyroid disease, who were in self-proclaimed good health and had at least one first or second degree relative with documented autoimmune hyper- or hypothyroidism. At study entrance, thyroid function tests revealed overt hyper- or hypothyroidism in 13 participants, leaving 790 subjects for follow-up (14). Subjects were seen annually at our institution during a 5-year follow-up.

At each visit, blood was withdrawn for thyroid function tests and the participants were asked to fill in questionnaires on smoking habits, pregnancy, estrogen treatment, and iodine excess in the previous year. Current smoking was defined as smoking now or having stopped smoking within 1 year before the study visit. Current pregnancy was defined as being pregnant at the time of the study visit, and postpartum as termination.
of pregnancy in the previous year. Current use of estrogens was defined as using estrogens at the time of the study visit, or having stopped taking estrogens in the previous year.

Endpoints of the study were either completion of the 5-year follow-up period or the development of overt hypothyroidism (defined as TSH > 5.7 mU/l and free thyroxine (FT4) < 9.3 pmol/l) or overt hyperthyroidism (defined as TSH < 0.4 mU/l and FT4 > 20.1 pmol/l), which were called cases or events. There occurred 38 cases of overt autoimmune hypothyroidism (34 with Hashimoto’s hypothyroidism and 4 with postpartum thyroiditis) and 13 cases of overt autoimmune hyperthyroidism (11 with Graves’ hyperthyroidism, 1 with postpartum thyroiditis, and 1 with silent thyroiditis), as reported elsewhere (15). In all subjects, except one, symptoms developed in between two annual visits to our center. These subjects consulted their family physician, and the diagnosis was confirmed clinically and biochemically. However, cases did not receive further follow-up for this study after the definitive diagnosis of overt AITD.

For each of these 51 cases two controls were selected from the remaining subjects in the cohort. Controls were matched for age at study entrance, and the analysis of their data was limited up to the same visit at which the cases had reached their endpoint, thereby guaranteeing that both the groups in this nested case–control study had been exposed to environmental factors for precisely the same follow-up period. The study was approved by the Institutional Review Board of the Academic Medical Center, University of Amsterdam, and all participants gave their informed consent prior to enrollment in the study.

**Laboratory measurements**

Serum TSH and FT4 were measured using time-resolved fluorimunoassays (Delfia hTSH and Delfia FT4 respectively, Wallac Oy, Turku, Finland). Reference values are for TSH 0.4–5.7 mU/l and for FT4 9.3–20.1 pmol/l as described previously (14).

Thyroid peroxidase (TPO) antibodies and thyroglobulin (Tg) antibodies were measured by chemiluminescence immunoassays (LUMI-test anti-TPO and LUMI-test anti-Tg respectively, Brahms, Berlin, Germany). Improved versions of both the assays became available during the follow-up: detection limits of these new assays were for TPO-Ab 30 kU/l and for Tg-Ab 20 kU/l. TPO-Ab concentrations obtained with the old assay were multiplied by a factor 0.72 to obtain comparative values in the new assay. TPO-Ab and Tg-Ab concentrations were considered to be positive at values > 100 kU/l. TSH receptor antibodies were determined as TSH binding inhibitory immunoglobulins (TBII) using the TRAK assay (Brahms); detection limits in the first and second generation TRAK assays were 5 and 1 U/l respectively, and values above 12 and 1.5 U/l respectively were considered as positive.

**Statistical analysis**

Statistical analysis was carried out with the SPSS 18 package (SPSS Inc., Chicago, IL, USA). Values are given as mean ± S.D. for age, but as median and interquartile range for all other parameters. Differences between cases and controls were evaluated by Student’s t-test for age, by the Mann–Whitney U test for TSH, FT4, TPO-Ab, and Tg-Ab, and by χ2 test or if appropriate Fisher’s exact test for the other parameters. A P value of < 0.05 was considered to indicate significant differences between the groups.

**Results**

The average time period between study entrance and the occurrence of an event was 3 years. At baseline, the 38 hypothyroid cases already had higher TSH, lower FT4, and higher TPO-Ab and Tg-Ab serum concentrations than their 76 controls, and the difference between both the groups persisted at 1 year before occurrence of the event (Table 1). No differences were observed in TSH, FT4, TPO-Ab, and Tg-Ab between study entrance and 1 year before the occurrence of event, neither among cases nor among controls. At baseline, 7 of the 38 subjects who had developed overt hypothyroidism had subclinical hypothyroidism. Exclusion of these 7 subjects from the analysis did not alter the results: the remaining 31 cases had still higher TSH, lower FT4, and higher TPO-Ab and Tg-Ab serum concentrations than their 62 controls, both at baseline and at 1 year before the occurrence of the event (data not shown).

In contrast, neither TSH nor FT4 values differed between the 13 hyperthyroid cases and their 26 controls at baseline or at 1 year before the event, but the prevalence of TPO-Ab and Tg-Ab was higher in cases than in controls (Table 1). TBII were present in only one participant at study entrance. No differences were observed in TSH, FT4, TPO-Ab, and Tg-Ab between study entrance and 1 year before the occurrence of event, neither among cases nor among controls. At baseline, 2 of the 13 subjects who had developed overt hyperthyroidism had subclinical hyperthyroidism. Exclusion of these 2 subjects from the analysis did not alter the results: TSH, FT4, TPO-Ab, and Tg-Ab serum concentrations in the remaining 11 cases and 22 controls were similar at baseline and at 1 year before occurrence of the event (data not shown). The difference in TPO-Ab and Tg-Ab concentrations was not significant between hypothyroid cases and hyperthyroid cases neither at baseline nor at 1 year before occurrence of the event.

Smoking status did not differ between cases and controls at study entrance or at 1 year before the event (Table 2). At the time of the event, however, there were fewer current smokers among hypothyroid cases than in controls (5 out of 38 (13%) cases versus 21 out
of 76 (28%) controls. \( P=0.083 \). This was not so in the hyperthyroid subgroup (2 out of 13 (15%) cases versus 7 out of 26 (27%) controls, \( P=0.7 \)).

Cases and controls did not differ with respect to pregnancies at study entrance or at 1 year before event, but there were more cases in the postpartum period than controls at the time of the event (Table 2). This was exclusively due to more hypothyroid cases in the postpartum period (8 out of 38 (21%) cases versus 3 out of 76 (4%) controls, \( P=0.006 \), but not due to more hyperthyroid cases (2 out of 13 (15%) cases versus 1 out of 26 (4%) controls. \( P=0.5 \). The proportion of women who had never been pregnant was lower in hyperthyroid cases than in their controls both at 1 year before the event and at the time of the event (1 out of 13 (8%) cases versus 10 out of 26 (38%) controls, \( P=0.063 \)); this was not so in the hypothyroid subgroup. The use of oral estrogens did not differ between cases and controls at any time (Table 2).

### Discussion

The aim of our case–control study nested in the observational Amsterdam AITD cohort study was to evaluate in a prospective manner the progression from euthyroidism to overt autoimmune hypo- or hyperthyroidism (called events or cases in the present study) and to examine the involvement of certain environmental factors in the development of the events. In our population, 51 cases were observed during the follow-up, consisting of 38 hypothyroid and 13 hyperthyroid events occurring on average 3 years after study entrance, as reported elsewhere (15). In our nested case–control study, controls had the same sex (all female) and by matching the same age and duration of the follow-up as the cases.

At study entrance, hypothyroid cases had higher TSH and TPO-Ab and lower FT4 serum levels than controls. This means that a minor degree of thyroid failure already existed at that time and that the transition from euthyroidism to autoimmune hypothyroidism had already started in the past. Although we do not know how long these abnormalities existed, it suggests that progression toward overt autoimmune hypothyroidism is a gradual process taking several years. This is in agreement with population studies focused on the evolution of subclinical hypothyroidism (defined as elevated serum TSH in the presence of normal FT4). In the Whickham survey (1), the annual rate of progression from subclinical to overt hypothyroidism was 3% in women with elevated TSH levels (> 6 mU/l), 2% in women with positive thyroid autoantibodies, and 4.3% when both elevated TSH and thyroid Abs were present. The importance of thyroid antibodies in the progression from subclinical to overt hypothyroidism was highlighted in other studies carried out in elderly subjects (2–8, 15). In a prospective study (9) in 107 subjects over the age of 55 with spontaneous subclinical hypothyroidism and no history of thyroid disease, it was found that TSH is the most powerful predictor for the outcome of spontaneous subclinical hypothyroidism.

At baseline, TSH and FT4 concentrations were not different between hyperthyroid cases and controls and

### Table 1 Comparison of characteristics between subjects who developed clinically overt autoimmune thyroid disease (AITD) and their corresponding controls (matched for age and duration of follow-up) at consecutive time points of follow-up in a nested case–control study of 153 women with first or second degree relatives with proven AITD derived from the prospective Amsterdam AITD cohort. Data are given as means ± s.d. or medians with interquartile range or proportions.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>TSH (mU/l)</th>
<th>FT4 (pmol/l)</th>
<th>TPO antibody (kU/l)</th>
<th>Tg antibody (kU/l)</th>
<th>TBII (+)</th>
<th>Cases ( n=38 )</th>
<th>Controls ( n=76 )</th>
<th>Cases ( n=13 )</th>
<th>Controls ( n=26 )</th>
<th>( P ) value</th>
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<tbody>
<tr>
<td>37</td>
<td>4.2 (2.7–5.7)</td>
<td>10.7 (9.7–11.6)</td>
<td>79%</td>
<td>75 (40–238)</td>
<td>0%</td>
<td>38 ± 12</td>
<td>12 ± 6</td>
<td>42</td>
<td>42 ± 13</td>
<td>0.96</td>
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<td>38 ± 12</td>
<td>1.6 (1.1–2.5)</td>
<td>12.8 (11.3–14.5)</td>
<td>0.001</td>
<td>8 ( &lt; 20–29)</td>
<td>1.00</td>
<td>0%</td>
<td>0%</td>
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<td>0%</td>
<td>0.97</td>
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<tr>
<td>42</td>
<td>1.6 (1.1–2.2)</td>
<td>13.3 (12.0–14.1)</td>
<td>&lt; 0.001</td>
<td>15%</td>
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<td>42 ± 13</td>
<td>1.5 (1.2–2.2)</td>
<td>14.1 (12.0–15.7)</td>
<td>&lt; 0.001</td>
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<td>42</td>
<td>1.5 (1.2–2.2)</td>
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<tr>
<td>0.001</td>
<td>545 ( &lt; 30–2265)</td>
<td>15%</td>
<td>560 ( &lt; 30–1742)</td>
<td>79%</td>
<td>46 (21–133)</td>
<td>10%</td>
<td>15%</td>
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<td>0.083</td>
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<td>42 ± 13</td>
<td>&lt; 30 (&lt; 30–155)</td>
<td>8%</td>
<td>&lt; 30 (&lt; 30–91)</td>
<td>&lt; 0.001</td>
<td>46 (21–133)</td>
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\( P \) value of cases versus controls. Time of event: visit when diagnosis was made or confirmed. FT4, free thyroxine; TPO, thyroid peroxidase; Tg, thyroglobulin; TBII, TSH-receptor antibodies.

*Fisher's exact test.
this was still true 1 year before the occurrence of the event. TPO-Ab concentrations were higher in hyperthyroid cases than in controls both at baseline and at 1 year before the occurrence of the event. Therefore, the biochemical switch from normal TSH and FT4 values to the suppressed TSH and elevated FT4 values must have occurred in the year before hyperthyroidism was diagnosed, suggesting that the transition from euthyroidism to overt autoimmune hyperthyroidism develops fast in terms of months rather than years. This observation is in agreement with a recent cross-sectional multicenter observational study (16), which investigated the duration of thyrotoxic symptoms until Graves’ hyperthyroidism was diagnosed. The median duration of Graves’ disease symptoms until diagnosis is 4 months. Some studies on patients with subclinical hyperthyroidism followed for 1–4 years suggested that subclinical hyperthyroidism...
may develop into overt hyperthyroidism at a rate of 1–5%/year (2, 10–13). However, these studies did not differentiate autoimmune subclinical hyperthyroidism from other causes of TSH suppression.

Our study results further suggest that certain environmental factors provoke the transition from euthyroidism to overt autoimmune hypo/hyperthyroidism.

In the present study, the proportion of current smokers was lower in hypothyroid cases than in controls but only at the time of the event, not at baseline or 1 year before the event. In view of the marginal statistical significance, the data must be interpreted cautiously that discontinuation of smoking promotes the development of hypothyroidism. This interpretation could be in line with recent observations that smoking protects against the development of TPO-Ab (17) and also against the development of hypothyroidism (18, 19). We could not ascertain the well-known risk of smoking for developing Graves’ hyperthyroidism, most likely to the small sample size (20).

Another potential factor is pregnancy. In the present study, cases were more often in the postpartum period at the time of the event than controls, which was seen only in the hypothyroid cases and due to the occurrence of postpartum thyroiditis. The proportion of women who had never been pregnant was lower in the hyperthyroid cases than their controls, that is, hyperthyroid cases had experienced pregnancies more often. This is in line with the notion that in the postpartum year the risk of developing Graves’ hyperthyroidism is higher (21, 22). The use of oral estrogens (oral contraceptive pills) was not related in our study to the occurrence of hypo- or hyperthyroidism, although a few studies in the past indicate a protective effect of estrogens on the development of hyperthyroidism (23, 24).

The limitation of our study is its sample size with a relatively low number of cases. The strength of our study is its prospective nature with annual assessments during 5-year follow-up. We are not aware of studies assessing the transition from euthyroidism to overt autoimmune hypo/hyperthyroidism in a structured, prospective manner.

Our observations led us to propose a model as depicted in Fig. 1 for the development of AITD. It is well accepted that AITD can be viewed as a complex disease arising from the interplay between a particular genetic background involving multiple genes and a variety of environmental factors (25). The so far identified susceptible genes can be divided into two major groups: the immune modulating genes (HLA-DR, CD40, CTLA4, and PTPN22) and the thyroid-specific genes (TG and TSHR) (26). Some polymorphisms confer susceptibility to both Graves’ and Hashimoto’s disease whereas others are specifically related to the risk of Graves’ or Hashimoto’s disease. Environmental factors play also an important role in the development of AITD, as the concordance rate for AITD in monozygotic twins is not 100% (27, 28). Twin studies suggest that genetic factors account for about 70% of the risk of developing AITD leaving about 30% for the environmental factors (27–30). Identified environmental factors are iodine intake, smoking, stress, pregnancy, estrogens, and possibly infections. It has been reported that in areas with sufficient iodine intake, hypothyroidism is more common than in iodine-deficient regions (31), whereas the overall prevalence of thyrotoxicosis is greater in iodine-deficient areas (32). Smoking is a risk factor for Graves’ disease (20). On the other hand, smoking decreases the risk on hypothyroidism (18, 19) and has a protective effect on the development of TPO-Ab and Tg-Ab (17). With regard to stress, several reports (33) showed that Graves’ patients have a higher number of stressful life events than controls in the months preceding the onset of the disease period but stress exposure has not been linked to the presence of thyroid antibodies (34).

In our view, Hashimoto’s hypothyroidism and Graves’ disease encompass a common entity and they are considered to represent the two ends of the same spectrum, i.e. AITD. Whether Graves’ or Hashimoto’s disease will develop in a subject will depend on a number of polymorphisms in susceptible genes and to a large extent to environmental factors (especially ambient iodine intake and smoking). Our study suggests that the transition from euthyroidism to Graves’ hyperthyroidism occurs relatively fast within 1 year in contrast to the transition from euthyroidism to Hashimoto’s hypothyroidism, which may take several years.
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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