The hormonal influence on the haemostatic system and the risk of thrombosis
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Incidence of Venous Thromboembolism in Patients with Overt Hyperthyroidism

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ABSTRACT

Background
Hyperthyroidism is associated with several changes in the haemostatic system resulting in a hypercoagulable state. It is uncertain at this stage whether this leads to an increased risk of venous thromboembolism (VTE). The aim of this retrospective cohort study was to determine the risk of VTE in all patients with overt hyperthyroidism and to compare this to the risk of VTE in the general population.

Methods
In three hospitals in the Netherlands, patients with biochemically confirmed hyperthyroidism caused by Graves’ disease, multinodular goiter or toxic adenoma were included. All available electronic and handwritten records were examined. Primary outcome was the occurrence of VTE within six months before and until six months after the diagnosis of hyperthyroidism.

Results
We included a total of 587 patients. Five patients experienced a VTE during the study period, resulting in an incidence rate of 8.7 (95% CI 2.8 – 20.2) per 1,000 person-years. Three of these five patients had a first VTE (incidence rate for first VTE was 5.3 [95% CI 1.1 – 15.6] per 1,000 person-years). Incidence rates of VTE in the general population are between 0.6 and 1.6 per 1,000 person-years for first VTE and 0.7 and 1.8 per 1,000 person-years for all VTE.

Conclusions
The incidence rate of VTE in patients with hyperthyroidism appears to be high. Future prospective studies are needed to further explore this possible association and to address its clinical implications.
**INTRODUCTION**

Venous thromboembolism (VTE) is the third most common cause of cardiovascular morbidity after stroke and myocardial infarction.\(^1\)\(^2\) VTE is a multifactorial disease for which numerous acquired and genetic risk factors are currently known.\(^3\)-\(^5\) Although the knowledge of risk factors has greatly expanded, it is still far from complete. Recent interest has focused on the association between thyroid dysfunction and VTE. Hyperthyroidism has been reported to cause a rise in plasma levels of von Willebrand factor (VWF) and coagulation factors VIII and IX and to enhance the formation of platelet plugs.\(^6\)-\(^10\) At the same time, fibrinogen levels are elevated,\(^6\),\(^9\),\(^11\) and fibrinolytic activity is decreased by an imbalance between tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1).\(^7\),\(^9\) Together these changes result in a hypercoagulable state which returns to normal after successful treatment of hyperthyroidism.\(^8\),\(^10\)

It remains unclear whether the hypercoagulable state in hyperthyroidism is reflected directly in an increased risk of VTE. In a previous case-control study, we found the risk of venous thrombosis to gradually rise with increasing levels of free thyroxine (FT4) within the reference range.\(^12\) However, from this study no definitive conclusions could be drawn with respect to hyperthyroidism, since the study population contained merely three patients with biochemical hyperthyroidism. So far only two studies investigated the association between hyperthyroidism and VTE. Their results are contradictory and both studies had methodological limitations,\(^13\),\(^14\) as they selected their study population by solely assessing diagnostic codes and did not differentiate between subclinical and overt hyperthyroidism.

We are planning a prospective trial to determine whether overt hyperthyroidism is associated with VTE. The aim of this pilot study was to obtain an estimate of the incidence rates of VTE before and after the diagnosis of hyperthyroidism. We selected all patients with proven overt hyperthyroidism during the preceding years in three hospitals in the Netherlands and registered VTE.
Methods

Study population

This retrospective cohort study was performed at the Academic Medical Center (AMC) of the University of Amsterdam, Leiden University Medical Center (LUMC) and the Slotervaart Hospital (SLZ), a general hospital in Amsterdam. In a study performed by our group we found a five-fold increased risk for FT4 levels > 24 pM compared to normal FT4 levels. Therefore we estimated an incidence rate of 5 per 1,000 person years in patients with overt hyperthyroidism. For that reason we strived to include at least 500 consecutive patients with a first episode of overt hyperthyroidism as a study cohort, preferably equally distributed among the three participating hospitals.

Identification of eligible patients was performed by searching the hospital’s electronic databases for specific diagnostic codes for hyperthyroidism: Graves’ disease (code 201), multinodular goiter (code 202), toxic adenoma (code 203) or hyperthyroidism not otherwise specified (code 204). The study period was intended to cover the period between January 1st 2005 and August 31st 2009.

However, since inclusion rates were lower in both the SLZ and LUMC, we decided to extend the study period within these hospitals from January 1st 2003 until August 31st 2009. In this way, the pre-defined number of patients was safeguarded while still maintaining an equal distribution between study centres.

Figure 1: Case identification procedure.

hCG = human chorionic gonadotropin; TSH = thyroid-stimulating hormone; VTE = venous thromboembolism
All available electronic and handwritten clinical records of identified patients were examined to confirm the presence and the cause of hyperthyroidism. We included all patients with a first episode of hyperthyroidism caused by Graves’ disease, multinodular goiter or toxic adenoma, diagnosed within the study period. Patients were excluded if aged below 18 years at the time of diagnosis, if hyperthyroidism (prior to treatment for thyroid dysfunction) was not confirmed with laboratory tests (e.g. subclinical hyperthyroidism), if it concerned a relapse of hyperthyroidism or if patients were referred from another medical facility for a second opinion.

By excluding cases of hyperthyroidism that were not confirmed with laboratory tests, we reduced the risk that patients with subclinical hyperthyroidism or hyperthyroidism treated months or years earlier would be included.

Definition of overt hyperthyroidism

Overt hyperthyroidism was defined biochemically as the concomitant presence of a thyroid-stimulating hormone (TSH) serum level below the lower limit of the local reference range and a FT4 serum level above the upper limit of the local reference range (before the start of treatment for thyroid dysfunction). Of note, as a result of alterations in assay techniques, the reference ranges for TSH were adjusted in two hospitals during the study period. Up to May 6th 2004 the reference range at SLZ was 0.40 – 3.40 mU/l and it was set at 0.35 – 4.70 mU/l from this date onwards. At the AMC, the reference range was changed from 0.40 – 4.00 mU/l to 0.50 – 5.00 mU/l from April 1st 2008 onwards. The reference range for TSH at the LUMC was 0.30 – 4.80 mU/l during the entire study period. Local reference ranges for FT4 were 10 – 23 pM (SLZ and AMC) and 10 – 24 pM (LUMC). We obeyed the reference range of each hospital during every specific period.

Data collection and outcome

Relevant data from all available patient records were documented by filling in a standardised Case Report Form (CRF) designed for this study. Patient records were systematically searched for the occurrence of VTE within six months prior to and six months after the diagnosis of hyperthyroidism. Diagnosis of VTE had to be confirmed by validated radiological imaging techniques, i.e. compression ultrasonography (CUS), phlebography, computed tomography (CT), pulmonary angiography or ventilation-perfusion scanning. In case of a VTE, the type, diagnostic method, established risk factors for and treatment of VTE were documented, as well as the thyroid function before and after the VTE. Additionally, the presence of established risk factors for VTE within three months prior to the event were noted, including surgery, trauma, malignancy, puerperium/pregnancy, prolonged bed rest (more than 3 days), use of estrogen/progesterone-containing agents, long-haul travel (more than 6 hours), Factor V
Leiden and protein C- or protein S-deficiency. In order not to miss any VTE, all patients’ general practitioners were addressed by letter and asked to fill in a standardised questionnaire on the occurrence of VTE according to the medical history of their patients, which they returned via a response envelope.

**Statistical analysis**

For descriptive statistics, categorical variables were expressed as numbers and percentages. Data of continuous variables were summarized using measures of central tendency (i.e. mean, median) and dispersion (i.e. standard deviation, range). For the incidence analysis, individual person times were computed by subtracting the entry date from the date of first VTE, end of follow-up or death, whichever occurred first. The entry date was considered as six months prior to the date of diagnosis of hyperthyroidism, whereas the end of follow-up was set at six months after this date. This meant that each patient maximally contributed one year to the total amount of person-years. Incidence rates were calculated by dividing the number of VTE events by the sum of the person-years. Separate incidence rates were calculated for first and all VTE in the whole study population. Stratified analyses were performed per gender. Incidence rates were presented per 1,000 person-years (95% confidence interval (CI)). Statistical analyses were performed by using the 18th edition of SPSS Statistics.

**Results**

Of 2,578 patients identified by screening diagnostic codes, 1,991 patients were excluded for reasons described in Figure 1, leaving a total of 587 patients (23%). Eighty percent (80%) of these 587 patients were female and the mean age was 46 years (range 18 – 92 years). Graves’ disease was the most common cause of hyperthyroidism, accounting for 87% of all cases. The majority of the patients were treated with medication alone (66%) or a combination of medication and radioactive iodine-therapy (28%). Surgical intervention was performed in 20 patients (3.4%), whereas one patient was not treated because of general health hazards. She died shortly after diagnosis of the hyperthyroidism. Within the follow-up period of six months after the diagnosis of hyperthyroidism, 90% of patients at least once had a FT4-level within the normal range. A total of 66% of all general practitioners responded to our questionnaire on the occurrence of VTE during the study period. No additional VTE were found via the questionnaire (Table 1).
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>468 (79.7)</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td></td>
</tr>
<tr>
<td>All, yrs (range)</td>
<td>46 (18-92)</td>
</tr>
<tr>
<td><strong>Etiology of hyperthyroidism</strong></td>
<td></td>
</tr>
<tr>
<td>Graves’ disease, n (%)</td>
<td>508 (86.5)</td>
</tr>
<tr>
<td>Multinodular goiter, n (%)</td>
<td>66 (11.2)</td>
</tr>
<tr>
<td>Toxic adenoma, n (%)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td><strong>TSH at diagnosis of hyperthyroidism</strong>, median (range)</td>
<td>&lt;0.02 mU/l (&lt;0.005 – 0.39)</td>
</tr>
<tr>
<td><strong>FT4 at diagnosis of hyperthyroidism</strong>, median (range)</td>
<td>35 pmol/l (23.2 - &gt;155)</td>
</tr>
<tr>
<td><strong>Treatment of hyperthyroidism</strong></td>
<td></td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td>387 (65.9)</td>
</tr>
<tr>
<td>Radioactive Iodine, n (%)</td>
<td>12 (2.0)</td>
</tr>
<tr>
<td>Medication + Radioactive Iodine, n (%)</td>
<td>167 (28.4)</td>
</tr>
<tr>
<td>Medication + Surgery, n (%)</td>
<td>15 (2.6)</td>
</tr>
<tr>
<td>Medication + Radioactive Iodine + Surgery, n (%)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>None, n (%)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Remission within 6 months after first visit</strong></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>531 (90.5)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>35 (6.0)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>21 (3.6)</td>
</tr>
</tbody>
</table>

*Remission is defined as free thyroxine level in the local reference range

TSH = thyroid-stimulating hormone; FT4 = free thyroxine

**Venous thromboembolism (VTE)**

Five patients (3 women, 2 men) experienced a VTE during the study period. Of these, one patient had a deep-vein thrombosis (DVT) of the leg, one had a pulmonary embolism (PE) without DVT, one had a jugular vein thrombosis and two had a combined DVT of the leg with a PE. Two of these patients had experience at least one VTE prior to the study period. Established risk factors for VTE were observed in four patients: three acquired and three genetic risk factors (Table 2).

In four patients, the VTE occurred prior to the diagnosis of hyperthyroidism (122, 42, 28 and 1 days), whereas in the remaining patient the VTE occurred six days hereafter (Fig. 2). Apart from this one patient that was diagnosed with hyperthyroidism and started treatment with anti-thyroid agents shortly before the VTE arose, information on thyroid function before the diagnosis of VTE was available for one other patient. This patient was diagnosed with subclinical hyperthyroidism 714 days before the VTE occurred, but was withheld from treatment. Hyperthyroidism was determined 28 days after the thrombosis occurred.
Table 2: Characteristics of VTE-cases.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex/Age</th>
<th>Cause of hyperthyroidism</th>
<th>Treatment of hyperthyroidism</th>
<th>Type of VTE</th>
<th>Diagnosis of VTE</th>
<th>Risk factors for VTE</th>
<th>VTE before/after hyperthyroidism</th>
<th>Thyroid function before VTE</th>
<th>Treatment of VTE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/35</td>
<td>Graves’ disease</td>
<td>Anti-thyroid drugs + radioactive iodine</td>
<td>DVT</td>
<td>CUS</td>
<td>Heterozygosity FVL, OCP-usage (since 3 months)</td>
<td>VTE 122 days before hyperthyroidism</td>
<td>Unknown</td>
<td>LMWH, phenprocoumon</td>
<td>Positive family history for VTE</td>
</tr>
<tr>
<td>2</td>
<td>F/45</td>
<td>Graves’ disease</td>
<td>Anti-thyroid drugs</td>
<td>DVT + PE</td>
<td>CUS</td>
<td>Heterozygosity FVL</td>
<td>VTE 42 days before hyperthyroidism</td>
<td>Unknown</td>
<td>LMWH, phenprocoumon</td>
<td>PE-development after 2 days of LMWH for DVT, MH: multiple DVTs and PEs</td>
</tr>
<tr>
<td>3</td>
<td>F/80</td>
<td>Multinodular goitre</td>
<td>Anti-thyroid drugs + radioactive iodine</td>
<td>Jugular vein thrombosis</td>
<td>CUS</td>
<td>None</td>
<td>VTE 28 days before hyperthyroidism</td>
<td>TSH &lt; 0.03 mU/l, FT4 21 pmol/l (714 days before VTE-diagnosis)</td>
<td>LMWH, acenocoumarol</td>
<td>Compression by intrathoracal goiter</td>
</tr>
<tr>
<td>4</td>
<td>M/52</td>
<td>Graves’ disease</td>
<td>Anti-thyroid drugs</td>
<td>DVT + PE</td>
<td>CUS/VQ-scan</td>
<td>Protein C-deficiency, Trauma (4 days before VTE)</td>
<td>VTE 1 day before hyperthyroidism</td>
<td>Unknown</td>
<td>LMWH, warfarin</td>
<td>MH: trombophlebitis, Positive family history for VTE</td>
</tr>
<tr>
<td>5</td>
<td>M/67</td>
<td>Graves’ disease</td>
<td>Anti-thyroid drugs + radioactive iodine</td>
<td>PE</td>
<td>CT</td>
<td>Bedrest/Immobility (hospital admission since 21 days)</td>
<td>VTE 6 days after diagnosis and start of treatment of hyperthyroidism</td>
<td>TSH 0.12 mU/l, FT4 40.5 pmol/l (6 days before VTE-diagnosis)</td>
<td>Heparin IV, phenprocoumon</td>
<td>PE during hospitalization with thrombosis prophylaxis (fraxiparine 2850IE SC daily)</td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; CUS = compression ultrasound; CT = computed tomography; VQ-scan = ventilation/perfusion-scan; FVL = factor V Leiden; OCP = oral contraceptive pill; TSH = thyroid-stimulating hormone; FT4 = free thyroxine; LMWH = low-molecular weight heparin; MH = medical history; IV = intravenously; SC = subcutaneously.
Figure 2: Occurrence of venous thromboembolism in relation to time of hyperthyroidism diagnosis. Every venous thromboembolic event is assigned a specific number, which are referred to in Table 2. VTE = venous thromboembolism; M = month
Incidence rates
The incidence rate of total VTE was 8.7 per 1,000 person-years (95% CI: 2.8 – 20.2) (5 cases). Men had a higher incidence rate than women. For men, the incidence rate was 17.4 per 1,000 person-years (95% CI: 2.1 – 61.4), whereas women had an incidence rate of 6.5 per 1,000 person-years (95% CI: 1.3 – 19.0). The incidence rate for first-ever VTE was 5.3 per 1,000 person-years (95% CI: 1.1 – 15.6) (3 cases) (Table 3).

Table 3: Incidence rates of VTE.

<table>
<thead>
<tr>
<th>Events</th>
<th>All</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>IR</td>
<td>CI (95%)</td>
<td>n</td>
<td>IR</td>
<td>CI (95%)</td>
<td>n</td>
<td>IR</td>
</tr>
<tr>
<td>Total VTE</td>
<td>5</td>
<td>8.7</td>
<td>2.8 – 20.2</td>
<td>3</td>
<td>6.5</td>
<td>1.3 – 19.0</td>
<td>2</td>
<td>17.4</td>
</tr>
<tr>
<td>First VTE</td>
<td>3</td>
<td>5.3</td>
<td>1.1 – 15.6</td>
<td>2</td>
<td>4.5</td>
<td>0.5 – 16.0</td>
<td>1</td>
<td>8.9</td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism; IR = incidence rate; CI (95%) = 95% confidence interval.

Discussion
In this retrospective cohort study that included 587 patients with a first episode of overt hyperthyroidism, we found an incidence rate of 8.7 per 1,000 person-years for all VTE and 5.3 per 1,000 person-years for first VTE. These rates are higher than those reported in the general population, where incidence rates for VTE vary between 0.6 and 1.6 per 1,000 person-years for first VTE and 0.7 and 1.8 per 1,000 person-years for all VTE. A direct comparison with our study population is difficult as incidence rates in our study could not be stratified by age due to the small number of events. Taking into account that the study population had a mean age of 46 years and the incidence of VTE in such a population generally is relatively low, our results suggest that the risk of VTE in patients with overt hyperthyroidism is increased.

There were established risk factors for VTE in four out of the five VTE-cases, underlining the multifactorial pathogenesis of VTE. Three of these four patients had acquired risk factors, thus these VTE can be considered provoked. Studies on the incidence rates of VTE in the general population most often report on provoked and unprovoked VTE combined, in which 50–55% of VTE are provoked. Regardless of the presence of risk factors, all VTE events are taken into account. The observed proportion of provoked VTE in our five cases (60%) is in accordance with the literature.
From these results, we hypothesise that hyperthyroidism might further add to the risk, thereby pushing the patient over the threshold for a thrombotic or embolic event. Previous studies on the association between hyperthyroidism and VTE showed contradictory results. These studies were based on patients selected by solely assessing diagnostic codes. The incidence of VTE in an American cohort was not affected by hyperthyroidism, whereas hyperthyroid patients in a Taiwanese population had a 2.3 times increased risk of PE in a five-year follow-up period. These studies were based on patients selected by solely assessing diagnostic codes. In contrast, with our specific and strict study design, all diagnostic codes of hyperthyroidism were thoroughly examined and hyperthyroid cases were only included if it concerned an overt hyperthyroidism, which had not been treated before the start of the study. Fifteen percent of the initially selected patients were excluded because of the absence of a laboratory confirmation of overt hyperthyroidism (Fig. 1). In other patients the first diagnosis of hyperthyroidism had taken place before the study period, or hyperthyroidism was the reason for a referral to one of the three participating hospitals. As we could only include 23% of all initially selected patients, our findings show that selecting patients by solely assessing diagnostic codes is imprecise. We can only speculate whether the bias in studies based on diagnostic codes alone lead to an over- or underestimation of the VTE risk in hyperthyroidism. If hyperthyroidism indeed would be established as a risk factor for VTE in future studies, the clinical relevance of such an association should be determined. First, it is likely that VTE occurring in relation to hyperthyroidism will be classified as provoked. This will influence the duration of VTE treatment. Second, a VTE should be considered as a possible first presentation of an underlying hyperthyroidism. Third, if in future studies the majority of thrombotic events are again diagnosed prior to hyperthyroidism, prevention of thrombosis in hyperthyroid patients probably is not very effective. We hypothesise that patients with hyperthyroidism have a higher risk of VTE before start of treatment than afterwards. Namely, high thyroxin levels, inducing a hypercoagulable state, are present for a longer period of time before diagnosis is made, as usually euthyroidism is reached within weeks after initiating antithyroid drugs.

Our study has certain limitations, which are inherent to all retrospective cohort studies. As the study design lacked regular hospital visits and we were dependent on the accuracy of treating physicians for all data collection, certain cases of VTE may have been missed. Examples of these are VTE diagnosed and treated in other, non-participating, medical centers. However, missing these VTE would only have resulted in an underestimation of our findings. Furthermore, as this study showed the inaccuracy of assigning diagnostic codes, we could have missed hyperthyroid patients that should have had one of the diagnostic codes we searched for but were wrongly assigned to another code. However, as this is most likely
not related to thrombosis risk, this will not have influenced our results. Another issue is that laboratory parameters on coagulation and fibrinolysis were missing, again due to the retrospective design of the study. Thus, we can not rule out the possibility that VTE is caused by an underlying auto-immunity. Four out of five patients with a VTE were diagnosed with Graves’ disease, which has an auto-immune origin. Theoretically, some of these patients may also have had an antiphospholipid syndrome,\textsuperscript{20–23} which increases the risk for VTE.\textsuperscript{5,20–22}

In conclusion, this pilot study provided us with an estimate of the incidence of VTE in hyperthyroid patients. To our knowledge, it was the first study that studied a population of only biochemically proven hyperthyroid patients. Both the incidence rates of first and all VTE in hyperthyroid patients exceeded the incidence of VTE in the general population in other studies, which suggests an increased risk. Prospective studies are necessary to further define the role of hyperthyroidism in the risk of VTE. Ultimately, this could lead to determining whether thromboprophylactic measures in hyperthyroid patients are useful and necessary, and whether the treatment of VTE associated with hyperthyroidism should be re-evaluated.

\textbf{Acknowledgements}

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Reference List


