Prothrombotic changes due to an increase in thyroid hormone levels

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Abstract

Objective
With increasing free thyroxine levels, a gradually rising risk of venous thromboembolism has been described in case-control studies. However, reports on the influence of thyroid hormones on haemostasis, while suggesting a hypercoagulable state in thyrotoxicosis, have often been inconclusive. The present study evaluates multiple markers of haemostasis and fibrinolysis in a paired design, making it more sensitive to changes in thyroid hormone levels.

Design
We analysed multiple variables in patients who shifted from severe hypothyroidism to mild hyperthyroidism during thyroid cancer treatment. Those with possible residual disease were excluded.

Methods
Ninety patients following total thyroidectomy were tested on two occasions: (a) before radioiodine remnant ablation and (b) 6 weeks later, on levothyroxine suppression treatment, and the results were compared using the Wilcoxon test for paired data.

Results
During levothyroxine treatment, significant increases (all p<0.001) in fibrinogen (from median 3.4 to 3.8 g/l), von Willebrand factor (from 85 to 127%), factor VIII (from 111 to 148%), and plasminogen activator inhibitor-1 (from 6.5 to 13.9 µg/l) were observed. In addition, the activation times of platelet adhesion and aggregation stimulated with collagen and epinephrine/adenosine diphosphate (ADP), i.e. closure times in platelet function analyzer (PFA-100), were significantly shortened (p<0.001): for epinephrine from median 148 to 117 s and for ADP from 95 to 80 s. Changes in other tests were less prominent or insignificant.

Conclusions
An increase in thyroid hormone levels shifts the haemostatic balance towards a hypercoagulable, hypofibrinolytic state. This may contribute to the increased cardiovascular morbidity and mortality observed even in mild thyrotoxicosis.
Introduction

With increasing free thyroxine (FT4) levels, a gradually rising risk of venous thromboembolism has been described in case-control studies (1, 2). However, reports on the influence of thyroid hormones on coagulation and fibrinolysis, while mostly suggesting a hypercoagulable state in thyrotoxicosis, have often been of low methodological quality (3-5). Indeed, no high-quality study was identified in a systematic review in 2007 (3). Since then only two studies (6, 7) were assessed as high-quality in a recent meta-analysis (5). Demir et al. (6) report a significant increase in plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (VWF) and fibrinogen following levothyroxine (LT4) suppression treatment for thyroid nodules. In their randomised crossover study in healthy volunteers van Zaane et al. (7) describe a dose-dependent effect of LT4 exposure on several variables of coagulation and fibrinolysis, the most prominent being an increase in PAI-1 (by 116%) and VWF activity and antigen (by 24% and 26%, respectively).

In this study, we employed a large cohort of patients treated with radioactive iodine 131-I (RAI) for differentiated thyroid cancer. In a short time they shifted from severe hypothyroidism (before thyroid remnant RAI ablation) to mild hyperthyroidism (due to LT4 suppression therapy), allowing analysis of their coagulation and fibrinolysis markers in a paired design. In addition, their primary haemostasis (i.e. platelet adhesion and aggregation) was assessed using the platelet function analyzer (PFA-100) (8), and compared in the same design.

Subjects and methods

Patients and study design

Differentiated thyroid cancer patients (n = 112), severely hypothyroid 4 to 5 weeks following total thyroidectomy without levothyroxine (LT4) replacement, were admitted for RAI thyroid remnant ablation. Before discharge, thyroid hormone suppression therapy (LT4 150 µg/day) was initiated and 6 to 8 weeks later they were examined in the outpatient follow-up clinic. Blood samples were taken on two occasions: (a) in severe hypothyroidism on admission, and (b) in mild (subclinical) hyperthyroidism on LT4 treatment. As cancer itself influences coagulation system we excluded 22 patients with possible residual disease, i.e. with measurable thyroglobulin (TG) level and/or positive anti-TG antibodies (TG-Ab) on follow up. This made our sample more homogenous and hopefully not influenced by the underlying cancer diagnosis. Accordingly, in 90 patients (13 men and 77 women, median age 54.1 years, interquartile range 39.2-64.0 years, 80 with papillary and 10 with
follicular cancer, all without residual disease), thyroid function tests, multiple coagulation and fibrinolysis tests, as well as the assessment of primary haemostasis using the PFA-100, were performed and analysed. Each patient gave his/her written informed consent and the investigation was approved by the ethical committee of our University Hospital. None of the patients had any previously known coagulation disorder, and none was treated with anticoagulants, antiaggregants or other medication capable of affecting coagulability.

Thyroid-related tests
Thyrotropin (TSH) was measured by immunoradiometric assay (IRMA, Immunotech, Beckman Coulter, Prague, Czech Republic). FT4, free triiodothyronine (FT3) and TG-Ab were determined by radioimmunoassays (RIA, Immunotech, Beckman Coulter). TG was assayed by immunofluorescence analysis (Thermo Scientific BRAHMS KRYPTOR, Hennigsdorf, Germany). The reference range (RR) for TSH, FT4 and FT3 is given in Table 1. The detection limit for TG was 0.8 µg/l, and TG-Ab were considered positive if > 100 IU/ml. The inter-assay coefficients of variation (CVs) were 5.5% for TSH, 8.4% for FT4, 6.4% for FT3, 5.6% for TG and 10.4% for TG-Ab.

Coagulation- and fibrinolysis-related tests
Fibrinogen was measured by clot-based assay – Clauss method (DG-FIB L Human, Diagnostic Grifols, Parets del Vallès, Spain); RR in Table 1. The limit of detection was 0.70 g/l. The intra-assay CVs were 3.20% (normal values) and 4.60% (pathological values), respectively. The inter-assay CVs were 4.30% (normal values) and 6.50% (pathological values), respectively.
Antitrombin was measured by chromogenic assay (BIOPHEN AT (LRT), Hyphen BioMed, Neuville-Sur-Oise, France); RR in Table 1. The limit of detection was ≤ 10%. The intra-assay CVs were 0.99% (normal values) and 1.38% (pathological values), respectively. The inter-assay CVs were 2.73% (normal values) and 0.57% (pathological values), respectively.
D-dimer was measured by immuno-turbidimetric method (STA - Liatest® D-Di, Diagnostica Stago, Asnières sur Seine, France); RR in Table 1. The limit of detection was 0.27 mg/l (FEU). The intra-assay and inter-assay CVs were 2.23% and 3.86% (pathological values), respectively.
Factor VIII was measured by one-stage method based on the Activated Partial Thromboplastin Time with deficient plasma (DG-FVIII, Diagnostic Grifols, Parets del Vallès, Spain; C. K. Prest®, Diagnostica Stago, Asnières sur Seine, France); RR in Table 1. The limit of detection was 1.3%. The intra-assay CVs were 6.40%
(normal values) and 6.90% (pathological values), respectively. The inter-assay CVs were 8.00% (normal values) and 8.40% (pathological values), respectively.

VWF was measured by immuno-turbidimetric method (STA - Liatest® VWF:Ag, Diagnostica Stago, Asnières sur Seine, France); RR in Table 1. The limit of detection was 3%. The intra-assay CVs were 1.90% (normal values) and 2.70% (pathological values), respectively. The inter-assay CVs were 2.90% (normal values) and 4.40% (pathological values), respectively.

PAI-1 antigen was measured by ELISA (ZYMUTEST PAI-1 Antigen, Hyphen BioMed, Neuville-Sur-Oise, France); RR in Table 1. The limit of detection was ≤ 0.5 ng/ml. The intra-assay and inter-assay CVs were 3-8% and 5-10%, respectively.

Platelet function analyzer (PFA-100) test

The process of primary haemostasis was measured by the PFA-100 System (Dade Behring, Vienna, Austria) using collagen/adenosindiphosphate (COL/ADP) and collagen/epinephrine (COL/EPI) cartridges. The principle of the test is flow of citrated whole blood through the cartridge containing a membrane coated with inductors (COL/ADP or COL/EPI); the output is closure time (CT) of the cartridge, reflecting velocity of platelet plug formation (8). The RR for PFA-100 System is given in Table 1, measuring range is 0-300 s and sensitivity and specificity is 96.1% and 88.6 %, respectively, and coefficient of accuracy is 0,979. The intra-assay CVs are 8.95 % for COL/ADP and 10.51% for COL/EPI and the inter-assay CVs are 0.6% for COL/ADP and 4.0% for COL/EPI.

Statistical analysis
For statistical analysis, SigmaStat software, version 3.1, was used. As data were mostly non-normally distributed
their summary values were expressed as median and interquartile range and comparisons were performed using
non-parametric Wilcoxon test for paired data. For the assessment of possible influence of age and body mass
index (BMI) on the observed changes, the whole sample was divided into tertiles and non-parametric analysis of
variance (Kruskal-Wallis test) was used.

Results

Table 1 summarizes the effects of LT4 treatment on coagulation and fibrinolytic parameters. Clearly significant
increases (p<0.001) were observed in procoagulation factors fibrinogen (median relative change 13%), VWF:Ag
(43%) and factor VIII (46%). The most prominent change observed was an increase by 100% in the
antifibrinolytic factor PAI-1:Ag. Though also significant but small increase in antithrombin (by 5%) and a less
significant (p=0.021) decrease in F1+2 (13%) was found the prevailing response to LT4 exposure was a shift
favouring prothrombotic over fibrinolytic events in the coagulation balance.

The activation times of primary haemostasis (i.e. platelet adhesion and aggregation), evaluated by the
PFA-100 closure times after stimulation with collagen and epinephrine or ADP, were significantly shortened,
median relative change being -15% for epinephrine and -21% for ADP. This also suggests a prothrombotic
change.

There was no significant influence of age and BMI on the observed significant changes (data not
presented).

We did not confirm a significant decrease in t-PA or an increase in D-dimer. Also, TAT was not
affected.

Discussion

Alterations in coagulation and fibrinolysis associated with abnormal thyroid hormone levels have recently been
reviewed (4, 5). While many studies suggest a trend towards a hypercoagulable state in thyrotoxicosis and a
hypocoagulable state in hypothyroidism, many reports are inconclusive and most of them were assessed as low-
to-medium methodological quality (3, 5). Two high-quality studies on the effect of thyroid hormone excess (6, 7)
have supported the prothrombotic shift in coagulation/fibrinolysis balance. Demir et al. (6) used LT4 suppression
treatment (0.05-0.15 mg/day for 1 year) in 30 women with nodular goitre and found a significant increase in fibrinogen (ca. 16%), D-dimer (ca. 23%), VWF (ca. 40%), tissue factor (ca. 43%) and PAI-1 (ca. 22%) levels; when the data was controlled for age and body mass index, only fibrinogen, VWF and PAI-1 remained significant. In the other study (7), healthy volunteers were given LT4 in a controlled randomized crossover pattern, and with the higher dose (0.45 or 0.6 mg/day for 14 days, n = 12) there was a significant increase in fibrinogen (ca. 17%), VWF activity (ca. 24%), VWF antigen (ca. 26%), factor VIII (ca. 19%), factor IX (ca. 14%), factor X (ca. 7%), PAI-1 (ca. 116%) and clot-lysis time (ca. 14%), while activated partial thromboplastin time was decreased by 3%. With the lower dose (0.3 mg/day for 14 days, n = 16), only the increase in VWF activity (7%) and VWF antigen (10%) remained significant.

Our study, while also addressing the question of LT4 effect on coagulation and fibrinolysis in a paired design, had several important differences from the above mentioned studies. First, the sample was larger (n = 90), which may have increased sensitivity. Second, our patients were treated for thyroid cancer, which may have affected some of the tests; we believe to have avoided this by excluding those with possible residual disease (using TG and TG-Ab). Third, our patients started the study in severe hypothyroidism (median TSH 109.6 mIU/l, FT4 < 2.4 pmol/l) and finished in mild hyperthyroidism (median TSH 0.14 mIU/l, FT4 23.9 pmol/l) whereas the patients in the first (6) and the volunteers in second study (7) started both euthyroid and finished either with values similar to ours (mean TSH 0.17 mIU/l, FT4 23.0 pmol/l), which also reflects a similar dose of LT4 (6), or in overt hyperthyroidism (median TSH 0.02 mIU/l, FT4 40.0 pmol/l) with the higher dose (6).

Fourth, the duration of our study was 6-8 weeks, rather reflecting rapid changes, which was similar to the second study (2 weeks) (7) but clearly different from the first one (1 year) (6).

Another well-designed study by Debeij et al. (9), though not mentioned in the comprehensive review by Stuijver et al. (5), addressed similar questions. Although smaller and primarily focused on the role of TSH in the observed coagulation abnormalities, it had important similarities, both in design and results. In 11 patients treated with suppression dose of LT4 following thyroid ablation for cancer (10 papillary and 1 follicular), LT4 was withdrawn for 4 weeks, leading to increased TSH (median 133.3 mIU/l) and decreased FT4 (median 1.5 pmol/l), and the first sample was taken for coagulation tests. Thereafter, LT4 treatment was restarted for 8 weeks, leading to suppressed TSH (median 0.7 mIU/l) and elevated FT4 (median 24.2 pmol/l) again, and the second sample was drawn. With the rapid shift from severe hypothyroidism to mild hyperthyroidism, they observed a significant rise in antithrombin (ca. 13%), factor II (ca. 7%), factor VIII (ca. 41%), factor IX (ca
32%), fibrinogen (ca. 19%) and VWF (ca. 41%) as well as a significant decrease in protein C (ca. 10%) and
factor VII (ca. 22%).

In spite of some methodological differences, the main results of the four studies were in reasonably
good accord. In all of them, a significant increase in fibrinogen and VWF was found in LT4-treated persons. The
increase in PAI-1 was clearly more prominent (and quantitatively greatest among the variables tested, ca. 100%)
in our study and in that by van Zaane et al. (7) than in Demir’s study (6). This may reflect either shorter duration
(weeks) or greater shift in thyroid hormone levels in the first two studies. In a similarly short study by Debeij (9),
PAI-1 was not assessed. Also, factor VIII was clearly increased in our study and in those by van Zaane (6) and
by Debeij (9) while it was not assessed by Demir et al. (6). Taken together, these results suggest that an increase
in thyroid hormone levels favours coagulation and suppresses fibrinolytic processes.

The increased levels of VWF and fibrinogen have been the most consistently found changes in
hyperthyroidism (4, 5). As these factors are closely related to platelet plug formation it may suggest an important
role of platelet – vascular wall interaction in the LT4 effect. The assessment of primary haemostasis using PFA-
100 thus seems to be a suitable method to address this question. Our finding that LT4 treatment shortened
closure time (CT) in the PFA-100, i.e. that LT4 activated platelet plug formation, lends further support to this
hypothesis. While the PFA-100 is widely used as a “global” test system for primary haemostasis in cardiology
and haematology (8), we have only found a single report on its use in abnormal thyroid function (10). Homoncik
et al. described a prolonged CT in hypothyroidism and shortened CT in hyperthyroidism (10). They also reported
a decrease in CT associated with an increase in T4 and VWF in the patients treated with LT4 for hypothyroidism
(mostly due to Hashimoto’s thyroiditis). Though their design was different the general pattern of the PFA-100
response to LT4 was similar in our larger study.

These results, together with a 100% increase in PAI-1, suggest an important role of endothelium
activation in thyroid hormone excess because both VWF and PAI-1 are synthesized in and secreted from
endothelium. Indeed, in their small (n = 14) study Burggraaf et al. (11) report an influence of hyperthyroidism on
some (e.g. VWF, t-PA, PAI-1, thrombomodulin), but not all (e.g. E-selectin), endothelium-associated proteins.
As human endothelial cells express thyroid hormone receptors alpha and beta-1 (12), endothelium seems to be an
important target for thyroid hormone action.

As for hepatically synthesized proteins, in their above mentioned study (11) Burggraaf et al. found an
increase in α2-antiplasmin and fibronectin, and a decrease in plasminogen while there was no significant change
in fibrinogen. Still, increased fibrinogen levels similar to ours have rather consistently been reported in other
studies (4,5), probably reflecting an increased hepatic synthesis due to thyroid hormone receptor-dependent transcriptional regulation demonstrated in hepatoma cell line (13). The increase in FVIII, observed in our study as well as in others (5), may have been due to the same process though not addressed in the hepatoma cell line study (13).

We conclude that the increase in thyroid hormone levels shifted the haemostatic balance towards a hypercoagulable and hypofibrinolytic state, namely due to an increased capacity of primary haemostasis (endothelium-platelet interaction) and a decreased capacity of fibrinolysis. However, none of our patients actually developed any clinical thrombotic event in the subacute setting. In addition, as there was no laboratory sign of actually occurring increase in coagulation (assessed by F1+2 and TAT) also no change in fibrinolysis (assessed by D-dimer) was observed.

The clinical importance of prothrombotic changes related to thyroid hormone excess has been a matter of controversy (4, 5). However, the updated meta-analyses of population cohort studies demonstrated a clear association of hyperthyroidism (even subclinical) with increased cardiovascular morbidity and mortality (14, 15). From combined community-based studies Yang et al. concluded that the general population with subclinical hyperthyroidism was at a 31% increased risk of cardiovascular disease (14). As nearly all the studies were adjusted for conventional cardiovascular risk factors (age, BMI, blood pressure, diabetes, cholesterol, and smoking), the results suggested that subclinical hyperthyroidism could be an independent risk factor for cardiovascular disease. Thrombotic events (both arterial and venous) related to thyroid hormone excess may partly explain this increased risk. Subclinical hyperthyroidism was associated with a 21% increased risk of coronary heart disease and a 68% increased risk of atrial fibrillation (15), which may be further complicated by stroke. Indeed, Schultz et al. reported an increased incidence of stroke among subjects with subclinical hyperthyroidism (hazard ratio 3.39; 95% CI 1.15-10.00, p=0.027), even after adjusting for sex, age, and atrial fibrillation (16). Also, an increased morbidity due to venous thromboembolism was observed (1, 2, 17). Though no controlled intervention studies confirming benefit of subclinical hyperthyroidism treatment are available (18), the recent guidelines advocate treatment, particularly in older patients (≥65 years) and those with clearly suppressed TSH (<0.1 mIU/l)(19).

In addition, the prothrombotic risk related to exogenous (even subclinical) thyroid hormone excess should be taken into consideration. Namely, LT4 overtreatment in hypothyroid patients that may occur rather frequently (20) should be avoided. Also for LT4 suppression treatment in thyroid nodules and differentiated
thyroid cancer (esp. low risk cases following surgery and RAI ablation), the risk/benefit considerations should include prothrombotic changes.

As a potential limitation of the study, its short duration may be considered. The study design was focused on the impact of a relatively rapid and pronounced change in thyroid hormone concentrations (within 6 to 8 weeks) on the observed variables, not allowing for extrapolation into further 6 months or later, which would be better related to clinical events. In fact, most published interventional studies on this topic, reviewed in (5), used a similar time pattern of weeks. However, chronic changes related to subclinical hyperthyroidism were observed by others. Demir et al. (6) report changes in fibrinogen, VWF and PAI-1 similar to ours after one year of LT4 suppression treatment for benign thyroid nodules. We therefore believe that at least some of the observed changes may be longer-lasting. Despite this limitation, our study possesses several strengths. The major strength is that the comparison is made within the patients themselves, so it is unlikely that other factors can explain the findings. Together with sample size (n = 90, i.e. much greater than studies reviewed in ref. 5) and homogeneity, this makes the results more reliable. In addition, the spectrum of tests was relatively wide, including those of primary haemostasis (PFA-100), which allowed us to suggest an important role of platelet/endothelium interaction in the observed effects. We believe that participation of thyroid hormones in this interaction deserves further research.

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.

Funding

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References


Table 1. The changes in haemostatic tests in 90 severely hypothyroid patients treated with suppressive dose of levothyroxine

<table>
<thead>
<tr>
<th>Variable (ref. range)</th>
<th>Hypothyroid</th>
<th>Mildly hyperthyroid</th>
<th>Relative change (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid function tests:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (0.15-5 mIU/l)</td>
<td>109.6 (78.6; 141.9)</td>
<td>0.14 (0.04; 0.50)</td>
<td>-99.9 (-100; -99.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT4 (11-25 pmol/l)</td>
<td>&lt;2.4 (&lt;2.4; &lt;2.4)</td>
<td>23.9 (22.1; 25.9)</td>
<td>&gt;895 (&gt;801; &gt;980)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT3 (2.5-5.8 pmol/l)</td>
<td>1.38 (1.08; 1.91)</td>
<td>5.12 (4.55; 5.60)</td>
<td>263 (162; 404)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Tests related to haemostasis and fibrinolysis (in order of relative change and significance):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothyroid</th>
<th>Mildly hyperthyroid</th>
<th>Relative change (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI-1:Ag (1-25 µg/l)</td>
<td>6.5 (4.2; 9.2)</td>
<td>13.9 (8.3; 23.5)</td>
<td>100 (44; 169)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Factor VIII (60-150%)</td>
<td>111 (78; 135)</td>
<td>148 (104; 203)</td>
<td>46 (7; 90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VWF:Ag (50-160%)</td>
<td>85 (70; 107)</td>
<td>127 (94; 153)</td>
<td>43 (23; 71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEPI-CT (75-145 s)</td>
<td>148 (119; 195)</td>
<td>117 (99; 145)</td>
<td>-21 (-38; -6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CADP-CT (62-104 s)</td>
<td>95 (80; 121)</td>
<td>80 (69; 96)</td>
<td>-15 (-33; 0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (2-4 g/l)</td>
<td>3.4 (2.7; 3.7)</td>
<td>3.8 (3.4; 4.2)</td>
<td>13 (6; 32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F1+2 (69-229 pmol/l)</td>
<td>222 (164; 294)</td>
<td>197 (149; 259)</td>
<td>-13 (-36; 21)</td>
<td>0.021</td>
</tr>
<tr>
<td>Antithrombin (80-120%)</td>
<td>100 (93; 110)</td>
<td>109 (100; 115)</td>
<td>5 (0; 11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t-PA:Ag (1-10 µg/l)</td>
<td>2.1 (1.5; 3.0)</td>
<td>2.0 (1.2; 3.1)</td>
<td>-5 (-29; 27)</td>
<td>0.380</td>
</tr>
<tr>
<td>D-dimer (0-0.5 mg/l)</td>
<td>0.32 (0.23; 0.48)</td>
<td>0.30 (0.24; 0.54)</td>
<td>0 (-21; 26)</td>
<td>0.463</td>
</tr>
<tr>
<td>TAT (2.0-4.2 µg/l)</td>
<td>3.0 (2.3; 5.0)</td>
<td>3.2 (2.7; 4.3)</td>
<td>8 (-39; 44)</td>
<td>0.941</td>
</tr>
</tbody>
</table>

TSH, thyroid stimulating hormone; FT4, free thyroxine, FT3, free triiodothyronine; PAI-1:Ag, plasminogen activator inhibitor-1 antigen; VWF:Ag, von Willebrand factor antigen; CEPI-CT, closure time with collagen/epinephrine in platelet function analyzer (PFA-100, see Methods); CADP-CT, closure time with collagen/ADP in PFA-100; F1+2, prothrombin fragment 1+2; t-PA:Ag, tissue-type plasminogen activator antigen; TAT, thrombin/antithrombin complex.

The values are expressed as medians with 1st and 3rd quartile in parentheses.

Wilcoxon rank sum test for paired data was used to assess the significance.