The hormonal influence on the haemostatic system and the risk of thrombosis
Stuijver, D.J.F.

Citation for published version (APA):
Stuijver, D. J. F. (2012). The hormonal influence on the haemostatic system and the risk of thrombosis

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Download date: 22 Dec 2018
The effect of subclinical hypothyroidism on vitamin K stability and sensitivity

Published in Thrombosis Research 2012;129:520-522

Alessandro Squizzato, Luca Galli, Bregje van Zaane, Erica Romualdi, Danka JF Stuijver, Francesco Dentali, Walter Ageno, Victor EA Gerdes
Abstract

Background
The effect of vitamin K antagonists (VKAs) is potentiated in overt hyperthyroidism and attenuated in overt hypothyroidism. Data on subclinical thyroid dysfunction and anticoagulation are lacking, in particular on subclinical hypothyroidism. The aim of this study is to explore the effect of subclinical hypothyroidism on VKAs sensitivity and stability.

Methods
Among 996 patients followed at the Anticoagulation Clinic, patients with subclinical hypothyroidism developed during VKAs treatment, who were treated with L-thyroxine and achieved an euthyroid state still on VKAs, were included in the study. VKAs sensitivity was calculated as median weekly dosage in mg. VKAs stability was measured as time spent in the therapeutic range (TTR). Weekly dosage and TTR were calculated during 6 and 12 weeks before objective diagnosis of subclinical hypothyroidism, during the first 6 and 12 weeks after L-thyroxine treatment was began, and during the first 6 and 12 weeks after objective euthyroidism has been reached.

Results
Twenty-six patients (8 males; median age 72.1 years) became subclinical hypothyroid during VKAs treatment. Main indication for anticoagulation was atrial fibrillation and two third of the patients had a target INR of 2.5. During a 6 weeks time interval, mean weekly dosage was 29.9 mg (±12.1 standard deviation [SD]) in subclinical hypothyroidism and 26.8 mg (±12.1 SD) in euthyroidism (P<0.05); median TTR was 61% (33-91 interquartile range [IR]) in subclinical hypothyroidism and 81% (51-100 IR) in euthyroidism (median difference = 13.5%; 95.2% confidence interval -8.5 to 30.5%). During a 12 weeks time interval, mean weekly dosage was 30.8 mg (±12.4 SD) in hypothyroidism and 27.0 mg (±12.7 SD) in euthyroidism (P< 0.05); median TTR was 54% (36-82 IR) in subclinical hypothyroidism and 65% (55-79 IR) in euthyroidism.

Conclusions
Data of our pilot study suggest that subclinical hypothyroidism may affect both VKAs stability and sensitivity. Given the high prevalence of thyroid disorders in the anticoagulated population, larger studies are urgently warranted.
**INTRODUCTION**

A large proportion of patients on vitamin K antagonists (VKAs) spend up to half of their time outside the therapeutic range, with resultant increased risk of either thromboembolic or bleeding complications.\(^1\) Age, concurrent medications, comorbidities, in particular heart failure, and patient’s compliance affect the quality of control of anticoagulant therapy in a predictable way. However, intraindividual variability in the response to VKAs remains often unexplained.\(^2\,^3\)

Thyroid disorders are common in patients on warfarin therapy, in particular because atrial fibrillation may be secondary to hyperthyroidism or because patients may develop amiodarone-induced dysfunction, either hypothyroidism or thyrotoxicosis.\(^4\) An influence of overt thyroid dysfunction on oral VKA sensitivity is well-known: the effect of VKAs is potentiated in thyrotoxicosis and attenuated in hypothyroidism.\(^5\) Data on subclinical hyperthyroidism suggest no significant impact on anticoagulation, but data on subclinical hypothyroidism are lacking.\(^6\)

The aim of this pilot study was to explore, for the first time, the effect of subclinical hypothyroidism on VKAs sensitivity and stability.

**METHODS**

**Study design and population**

All patients followed at the Anticoagulation Clinic of the Department of Clinical Medicine of the University Hospital of Varese, Italy, at December 2009 and treated with the two available oral VKAs, i.e. warfarin and acenocoumarol, were potentially eligible. One investigator (LG) retrospectively reviewed electronic and medical records to identify a past or present history of subclinical hypothyroidism. Patients were included if they fulfilled all three of the following criteria: 1. subclinical hypothyroidism occurred during VKAs treatment; 2. treatment with levothyroxine while on VKAs; and 3. achievement of an euthyroid state while on VKAs. Thyroid hormone levels in these three periods were directly provided by patients or retrieved in the electronic database of the Nuclear Medicine Laboratory.

Patients were considered eligible with both naïve subclinical hypothyroidism and subclinical hypothyroidism due to an insufficient replacement therapy with levothyroxine. All target international normalized ratio (INR) and VKAs indications were included.
Definition of subclinical hypothyroidism and laboratory assay

Subclinical hypothyroidism was biochemically defined by increased serum TSH concentration in the presence of normal serum FT4 and/or FT3 concentrations. Serum free thyroxine (FT4; FT4 RIA, Brahms, Germany), free triiodothyronine (FT3; FT3 SPART RIA, Brahms), thyrotropin (TSH; TSH-CTK-3, DiaSorin, Italy), were assayed by commercial methods. Reference values in our laboratory are as follows: FT4, 0.75 – 1.90 ng/dl; FT3, 1.50 – 5.30 pg/ml; TSH, 0.31 – 4.50 mU/l. Thyroid autoantibodies and antiphospholipid antibodies were not routinely checked.

Statistical analysis

Normal distribution of collected data was explored with Shapiro-Wilk test. If normally distributed, the paired t-test for mean value was applied; if not, the non-parametric Wilcoxon signed ranks test was used. A P-value < 0.05 was considered statistically significant. VKAs sensitivity was calculated as mean weekly dosage in mg. To include also patients on acenocoumarol, given that a validated transformation coefficient is not available, we considered 1 mg of acenocoumarol as equivalent to 2 mg of warfarin. VKAs stability was measured as time spent in the therapeutic range (TTR), estimated by linear interpolation between successive INR measurements, calculating the proportion of time during each interval that was spent in-range, summing across all intervals, and then dividing by the total duration of therapy. Weekly dosage and TTR were calculated during 6 and 12 weeks before objective diagnosis of subclinical hypothyroidism or suboptimal replacement therapy (phase A), during the first 6 and 12 weeks after levothyroxine treatment was began or the levothyroxine dose was altered (phase B), and during the first 6 and 12 weeks after objective euthyroidism had been reached (phase C). A period of six and 12 weeks was arbitrary selected to identify a period at high probability to be in the defined thyroid state. In case of vitamin K interruption for a dental, invasive or surgical procedure, TTR was not calculated or an adjacent period was included. Analyses were performed with PARMA 5.7 (Instrumentation Laboratory, Italy), and with StatsDirect 2.7.2 (StatsDirect Ltd, United Kingdom).

RESULTS

Overall, 996 patients were on VKA, and 118 (11.8%) had thyroid disease. Sixty-seven had hypothyroidism (57%), 16 hyperthyroidism (14%) and 35 (30%) a thyroid disease without abnormal hormone levels (e.g. multinodular goiter). Twenty-six patients (8 males; median age 72.1 years) had an episode of subclinical hypothyroidism during VKA treatment and objective data on thyroid disease available. Half of the patients had a Hashimoto’s thyroiditis and the other half an iatrogenic cause of subclinical hypothyroidism (Table 1). Two third of the patients have never been treated with levothyroxine. Main indication for anticoagulation
was atrial fibrillation and two third of the patients had a target INR of 2.5. Almost 70% of this population was on chronic therapy with 3 or more drugs other than VKAs and levothyroxine.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Subclinical hypothyroidism (n=26)</th>
<th>Male, n (%)</th>
<th>Age, median (IR), years</th>
<th>VKA</th>
<th>Warfarin 21 (81)</th>
<th>Acenocoumarol 5 (19)</th>
<th>INR target</th>
<th>2.5 20 (77)</th>
<th>3.0 6 (23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary indication for anticoagulation therapy*</td>
<td>Atrial fibrillation, n (%) 13 (50)</td>
<td>Venous thromboembolism, n (%) 3 (11.5)</td>
<td>Heart valve prosthesis, n (%) 6 (23.1)</td>
<td>Antiphospholipid syndrome, n (%) 3 (13.9)</td>
<td>Severe dilatatative cardiomyopathy, n (%) 1 (3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On chronic therapy with 3 or more drugs other than VKA and levothyroxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 (69)</td>
<td></td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis, n (%)</td>
<td>13 (50)</td>
<td>Iatrogenic, n (%)</td>
<td>13 (50)</td>
<td>Amiodarone, n (%)</td>
<td>9 (35)</td>
<td>Surgical, n (%)</td>
<td>2 (8)</td>
<td>Radioiodine, n (%)</td>
</tr>
<tr>
<td>Type of hypothyroidism</td>
<td>Naïve patient, n (%)</td>
<td>18 (69)</td>
<td>Insufficient levothyroxine treatment, n (%)</td>
<td>8 (31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time interval between VKA start and objective subclinical hypothyroidism diagnosis (median and IR, months)</td>
<td>14.2 (5.5-87.1)</td>
<td>Time interval between levothyroxine start and euthyroidism* (median and IR, months)</td>
<td>8.1 (2.9-15.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: VKA, vitamin K antagonist; n, number; IR, interquartile range; SD, standard deviation

*Three patients had more than one disease requiring vitamin K antagonist

° Euthyroidism was defined as the first period of 6 and 12 weeks in which thyroid hormones were within the normal ranges and treatment with VKA had not been interrupted.
In some patients, co-medication was altered during one of the analyzed time intervals. Methimazole was stopped and prednisone was introduced in one patient during subclinical hypothyroidism. Two patients received a brief course of antibiotics during levothyroxine treatment. In the euthyroid phase, to the same patient whose therapy was modified in hypothyroidism lovastatin and glicazide were added, allopurinol was started in another patient and double antiplatelet therapy (clopidogrel plus aspirin) was introduced in a third patient. Other baseline characteristics were summarized in Table 1.

During a 6 weeks time interval, mean weekly dosage was 29.9 mg (±12.1 standard deviation [SD]) in subclinical hypothyroidism and 26.8 mg ((±12.1 SD) in euthyroidism (P<0.05); median time spent in the therapeutic range was 61% (33-91 interquartile range [IR]) in subclinical hypothyroidism and 81% (51-100 IR) in euthyroidism (median difference 13.5%; 95 % confidence interval for difference between population medians: - 8.5% to 30.5%).

During a 12 weeks time interval, mean weekly dosage was 30.8 mg (±12.4 SD) in subclinical hypothyroidism and 27.0 mg (±12.7 SD) in euthyroidism (P< 0.05); median time spent in the therapeutic range was 54 % (36-82 IR) in subclinical hypothyroidism and 65 % (55-79 IR) in euthyroidism. A statistically significant difference in mean weekly dosage was shown also between the first period of replacement therapy with levothyroxine (phase B) and euthyroidism, but no difference was detected between subclinical hypothyroidism and the first period of replacement therapy with levothyroxine (Table 2 and 3).

**Table 2. Vitamin K sensitivity (mean weekly dosage and standard deviation)**

<table>
<thead>
<tr>
<th></th>
<th>Subclinical hypothyroidism (phase A)</th>
<th>Levothyroxine treatment (phase B)</th>
<th>Euthyroidism (phase C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n 6 weeks 12 weeks</td>
<td>n 6 weeks 12 weeks</td>
<td>n 6 weeks 12 weeks</td>
</tr>
<tr>
<td>25a</td>
<td>29.9 mg ± 12.1b 30.8 mg ± 12.4c</td>
<td>24a 29.3 mg ± 13.0d 28.1 mg ± 13.0e</td>
<td>23 26.8 mg ± 12.2 27.0 mg ± 12.7 2-æ</td>
</tr>
</tbody>
</table>

n, number of patient with available data
  a for 6 weeks, data available for all 26 patients
  b P< 0.05
Table 3. Vitamin K stability (median time spent in the therapeutic range and interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Subclinical hypothyroidism (phase A)</th>
<th>L-thyroxine treatment (phase B)</th>
<th>Euthyroidism (phase C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n 6 weeks 12 weeks</td>
<td>n 6 weeks 12 weeks</td>
<td>n 6 weeks 12 weeks</td>
</tr>
<tr>
<td></td>
<td>25 a 61 % (33-91)b</td>
<td>24 a 67 % (46-89)</td>
<td>23 81 % (51-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 % (36-82)</td>
<td>65 % (55-79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62 % (52-84)</td>
<td></td>
</tr>
</tbody>
</table>

n, number of patient with available data

a for 6 weeks, data available for all 26 patients

b \( P=0.27 \) compared to euthyroidism

**DISCUSSION**

Our pilot study suggests that subclinical hypothyroidism has an effect both on VKA stability and sensitivity. During subclinical hypothyroidism patients had a diminished sensitivity to VKAs in comparison with the euthyroid state, both considering a 6 and 12 weeks time interval. This is in line with previous literature on overt hypothyroidism. We also noted a clear trend for decreased VKAs stability in subclinical hypothyroidism relative to the euthyroid state.

The effect of overt thyroid dysfunction on VKAs sensitivity has been studied in the past. This disease-drug interaction has been described in a number of case reports and in animal studies in which a change in thyroid function was associated with a change in warfarin sensitivity, irrespective of the nature of the underlying thyroid disease: overt hyperthyroidism potentiated and overt hypothyroidism diminished the effect of VKAs. Practically, it means that overt hypothyroid patients require higher dosages to reach target INR, and vice versa for overt hyperthyroidism. As the pharmacokinetic parameters – plasma clearance, volume of distribution, plasma protein binding – were unaffected by thyrotoxicosis, warfarin potentiation was thought to reflect an enhanced pharmacodynamic effect.

Data on subclinical thyroid dysfunction and anticoagulation are sparse. To the best of our knowledge, only one study was published on patients with subclinical hyperthyroidism and our study is the first to investigate the effect of subclinical hypothyroidism on VKAs sensitivity and stability. Bucerius and colleagues studied 178 patients with subclinical hyperthyroidism.
undergoing iodine-131 therapy for a benign thyroid disease that were on VKAs with an INR target range of 2 to 3. Apparently, they did not find any influence of subclinical state on the stability of VKA therapy. However, they did not measure time spent in the therapeutic range and no data on VKAs sensitivity were provided.

The clinical impact of our findings is potentially relevant. In our population of anticoagulated patients, more than 10% had a thyroid disease. Overt and subclinical hyperthyroidism may cause atrial fibrillation and their treatment may cause a temporary hypothyroid state. Thyroid blocking agents, such as methimazole, and antiarrhythmic drugs for atrial fibrillation modify oral VKA sensitivity. In particular, amiodarone causes an increased sensitivity to warfarin which causes an increased INR at the beginning of therapy. Beyond the predictable pharmacokinetic drug-drug interaction requiring a significant warfarin dose reduction, the iodine-rich amiodarone affects the thyroid gland, causing overt or subclinical hypothyroidism or thyrotoxicosis in more than 10% of cases.

Besides these relationships, subclinical hypothyroidism characteristics make our findings potentially of great impact. The prevalence of subclinical hypothyroidism in the adult population is about 4% to 8.5% in those without known thyroid disease. The prevalence increases with age, and in women older than 60 years, subclinical hypothyroidism is present in up to 20%. Subclinical hypothyroidism has no or few mild symptoms, and it usually cannot be recognised without thyroid hormone measurement. Therefore, patients may be at risk of INR fluctuations for several months. Moreover, when diagnosed, not every patient is routinely treated with Levothyroxine. Finally, patients already on levothyroxine often have periods of subclinical hypothyroidism due to an insufficient dosage.

This study has some limitations. The included population is certainly underpowered to draw any definitive conclusions. We regard these data as hypothesis generating and useful for sample size calculations for future studies. Drug administration or withdrawal are well-known factors that may influence the quality of control of anticoagulant therapy and VKAs sensitivity, and were not taken into account in the analysis. However, these factors were more prevalent in the euthyroid state. Moreover, as warfarin was self-administered, drug compliance was not specifically taken into account. Given the retrospective design of the study, it is probable that each patient had the same compliance in both hypothyroid and euthyroid state, and there is no reason to believe that the beginning of levothyroxine may increase patients compliance to VKAs.
In conclusion, our pilot study clearly suggests that subclinical hypothyroidism may have an effect both on VKAs stability and sensitivity. Even if future studies are needed to definitely conclude on this topic, it is plausible that some unstable patients on VKAs have a (subclinical) thyroid hormone excess or deficiency.

**Reference list**

7. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease. Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–238.