Thyroid disease and haemostasis: a relationship with clinical implications?
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The interactions between dysfunctional thyroid diseases and haemostasis are the main focus of the thesis. After the introduction and outline, Chapter 2 gives an overview on the complex interactions of hormones with the coagulation and fibrinolytic system. The thesis is divided into two parts. The first part (Chapters 3-11) is focused on the effect of thyroid hormone on laboratory markers of coagulation and fibrinolysis, and venous thromboembolism; the second part (Chapters 12-15) addresses the influence of thyroid disorders on vitamin K antagonists.

**Part I: Thyroid, coagulation and fibrinolysis, and venous thromboembolism**

In Chapter 3, 4 and 5 we review the available evidence on the effects of hyperthyroidism and hypothyroidism on these systems, on the association between hypothyroidism and acquired von Willebrand’s syndrome, and the relationship between thyroid diseases and cerebrovascular diseases. In Chapter 3, we systematically summarise and analyse all published case-control or interventional cohort studies that evaluated the effects of hyperthyroidism and hypothyroidism on the coagulation-fibrinolytic system in vivo that were identified by a computer-assisted search of the MEDLINE and EMBASE electronic databases. A total of 36 papers were included. No high quality study was identified. A total of 19 tests were investigated in the medium-quality studies. These tests indicate a hypocoagulable state for overt hypothyroidism and a hypercoagulable state for overt hyperthyroidism.

In Chapter 4, we systematically describe all published clinical epidemiological and interventional studies, case reports and in vitro studies that investigated the association between hypothyroidism and acquired von Willebrand’s syndrome that were identified by a computer-assisted search of the MEDLINE and EMBASE electronic databases. A total of 41 papers were included. No high quality in vivo study was identified. Almost all bleeding episodes described in the case reports were mucocutaneous bleedings, and we describe the range of the observed low levels of von Willebrand factor antigen VWF activity and factor VIII activity. Acquired von Willebrand’s syndrome may be the main factor responsible for bleeding diathesis in overt hypothyroid patients.

Chapter 5 summarises certain and possible cerebrovascular complications of thyroid disorders. In overt hyperthyroidism, cardioembolic stroke is clearly associated to thyrotoxic atrial fibrillation, and in subclinical hyperthyroidism with serum thyroid-stimulating hormone levels <0.1 mU/L, the incidence of atrial fibrillation is increased. In vitro and in vivo studies indicate a hypercoagulability state in hyperthyroidism and case reports suggest an increased risk of acute cerebral venous thrombosis. Possible associations between hyperthyroidism and Moyamoya or Giant cell arteritis have only been described in case reports. There is enough evidence that overt hypothyroidism is associated with several traditional and newer atherosclerotic risk factors, especially hypertension, hyperlipidemia, and hyperhomocysteinemia. For subclinical hypothyroidism, these associations are less certain.

Chapter 6 is the first published study that evaluated the relationship between thyroid dysfunction and a deep venous thrombosis (DVT). Fifty consecutive adult outpatients with a previous diagnosis of provoked DVT, 50 consecutive adult outpatients with a previous diagnosis
of unprovoked DVT, both of the lower legs, and 50 control subjects were enrolled. Previously unrecognized subclinical hypothyroidism was diagnosed in seven (14.0%) unprovoked DVT patients, one (2%) provoked DVT patient, and one (2%) control. The results of this pilot study suggest an increased prevalence of subclinical hypothyroidism in patients with unprovoked DVT.

In Chapter 7, parameters of thyroid function were assessed in 190 venous thrombosis cases on the day of the diagnosis of thrombosis and 379 sex-matched controls. We found the risk of venous thrombosis to gradually rise with increasing levels of free thyroxine. In the absence of traditional acquired risk factors, free thyroxine levels above 17 pmol/L yielded a sex- and age-adjusted odds ratio (OR) of 2.2 (95% confidence interval [CI] 1.2-4.2) for deep venous thrombosis, which further increased up to an OR of 13.0 (95% CI 1.1-154.1) for free thyroxine levels above reference range. These data suggest increasing levels of free thyroxine to be a risk factor for venous thrombosis.

The risk of pulmonary embolism (PE) during thyroid dysfunction were tested in Chapter 8 with a nested case-control study using the PHARMO Record Linkage System, a Dutch population-based registry that links medication histories to hospital admission records. New use of antithyroid or thyreomimetic agents, and thyroid-related hospitalizations, were also used as indicators for diagnosis of thyroid disease. The study population consisted of 3479 cases admitted to the hospital for PE and 11830 controls. Diagnosis of hypothyroidism prior to the index date, i.e. treated hypothyroidism, was significantly associated with PE (OR 2.05, 95% CI 1.11-3.78), especially within the first three months after diagnosis (OR 4.98; 95% CI 1.39-17.82). No association was found for diagnosis of hypothyroidism after the index date. Our findings suggest that patients with hypothyroidism are at increased risk of pulmonary embolism and it is probably related to treatment with thyreomimetic agents rather than hypothyroidism itself. There were only few patients who used antithyroid agents. As a result we were not able to draw strong conclusions about hyperthyroidism before or within the first months after PE although the data suggest an association within the first months after diagnosis.

In Chapter 9, the effect of supraphysiological doses of levothyroxine on coagulation and fibrinolysis was tested in healthy volunteers randomized to receive levothyroxine or no medication for 14 days in a crossover design. 16 participants received levothyroxine in a dose of 0.3 mg/day, and 12 received levothyroxine 0.45 or 0.6 mg/day depending on body weight. Levels of von Willebrand factor activity and antigen, factor VIII, factor IX, factor X, fibrinogen, PAI-1 and clot-lysis time higher compared to no medication and activated partial thromboplastin time were decreased. Overall data suggest that thyroid hormone excess increases coagulation factor levels, and inhibits fibrinolysis, in a dose-dependent fashion.

The effect on thrombin-activatable fibrinolysis inhibitor (TAFI) was specifically addressed in another study, described in Chapter 10. The effect of hyperthyroidism on TAFI was studied in the same patients of Chapter 9. The effect of hypothyroidism on TAFI was studied in a multicenter observational cohort study. Blood was drawn before treatment of patients with newly diagnosed hypothyroidism and when euthyroidism was achieved. Hyperthyroidism resulted in a hypofibrinolytic condition and in an enhanced TAFIa-dependent prolongation of clot-lysis. Hypothyroidism resulted in hyperfibrinolysis.
and a reduced TAFIa-dependent prolongation of clot-lysis.

In Chapter 11, the case of a young woman who attempted suicide by intoxication with 25 mg of levothyroxine was presented. Levels of thyroid hormones and parameters of coagulation and fibrinolysis were assessed in the days following the auto-intoxication. We found a marked increase in levels of coagulation factors VIII, IX and X, von Willebrand factor and plasminogen activator inhibitor-1, resulting in enhanced thrombin generation. These findings, similarly to the previous ones, suggest that thyroid hormone excess shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state, and is therefore likely to reflect an increased risk of venous thrombosis.

Part II: Thyroid and vitamin K antagonist

Chapter 12 is a published editorial in which we commented the available evidence on the relation between thyroid dysfunction and vitamin K antagonist, and highlighted the lack of published studies, in particular for subclinical hypo- and hyperthyroidism, even if the old literature provided a solid pathophysiological rationale.

To fill the gap of the literature and to explore the role of thyroid autoantibodies, we tested in two pilot studies the effect of subclinical hypothyroidism on vitamin K stability and sensitivity and the effect of thyroid autoantibodies on warfarin stability.

In Chapter 13, 26 patients with subclinical hypothyroidism occurring during vitamin K antagonist treatment, who were treated with L-thyroxine and achieved an euthyroid state still on vitamin K antagonist treatment, were included in the study. Weekly dosage and time spent in the therapeutic range 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. During a 6 weeks time interval, mean weekly dosage was 29.9 mg during subclinical hypothyroidism and 26.8 mg during euthyroidism (P<0.05); median time spent in the therapeutic range was 61% during subclinical hypothyroidism and 81% during euthyroidism (median difference = 13.5%; 95.2 % CI -8.5 to 30.5%). Data of our pilot study suggest that subclinical hypothyroidism may affect both VKAs stability and sensitivity.

In Chapter 14, 36 patients, 12 with elevated antibody levels and 24 with normal antibody levels with available INR values were analysed. Stability of oral anticoagulation was evaluated during a period of three months, before or after the date of antibody measurement, and presented as the percentage of time in range and the standard deviation of the mean INR values Percentage of time in range was slightly lower in patients with elevated antibodies (61.9% vs 70.1%, p=0.16), whereas the standard deviation of the INR values was higher in patients with elevated antibodies (0.83 vs 0.65, p=0.05), suggesting that thyroid autoantibodies may be responsible for the instability of the INR control.

Finally, in Chapter 15, we present the case of an elderly man with a recurrent episode of deep venous thrombosis during optimal oral vitamin K antagonist treatment, associated with a new diagnosis of overt hyperthyroidism, with no evidence of occult cancer and normal levels of antiphospholipid antibodies.