Hormones, haemostasis, and the risk of thrombosis
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This thesis describes the relationship between hormones, haemostasis, and clinical manifestations of thrombosis, both venous and arterial. The thesis consists of three parts. The first part concerns the role of thyroid hormone, the second part involves the glucocorticoid hormone cortisol, and the third part focuses on the effect of prolactin.

In Chapter 2, the available evidence on the influence of pituitary, adrenal, and parathyroid hormones on the coagulation and the fibrinolytic systems is reviewed. The possible clinical implications of endocrine disorders are additionally addressed. An effect on markers of coagulation and fibrinolysis has been shown for hyperprolactinaemia, growth hormone excess and deficiency, endogenous and exogenous hypercortisolism, pheochromocytoma, primary hyperaldosteronism, and hyperparathyroidism, but the evidence is not particularly robust. To date, sufficient evidence on the clinical relevance of the induced haemostatic abnormalities only exists for Cushing’s syndrome, i.e. patients with Cushing’s syndrome have repeatedly been proven to be at increased risk of venous thrombosis.

Chapter 3 details the contribution of thyroid hormones, cortisol, the somatotropic hormones, and prolactin in the development of atherothrombosis. The epidemiological evidence on the association between hormones and cardiovascular disease, such as stroke and myocardial infarction, is discussed, and possible pathophysiological mechanisms underlying this association are addressed. Hormones can contribute to the development of cardiovascular disease both indirectly by inducing secondary metabolic changes such as hypertension, insulin resistance, or dyslipidaemia; and directly by modulation of cellular pathways that are important in the process of atherosclerotic plaque formation (atherogenesis), plaque instability, and thrombosis. To date, several new therapeutic approaches which focus on the control of hormones at tissue level, independently of their circulating levels, are being developed. This may offer new possibilities for cardiovascular risk reduction.

Part I: Thyroid hormone
Chapter 4 describes the results of a controlled, randomised, crossover study on alterations in coagulation and fibrinolysis after exposure to supraphysiological doses of levothyroxine. To study the effects of different degrees of thyroid hormone excess, 16 participants received levothyroxine in a dose of 0.3 mg per day, and 12 received levothyroxine 0.45 or 0.6 mg per day depending on body weight. Parameters of coagulation and fibrinolysis were assessed before and after 14 days of levothyroxine exposure, and compared to a medication-free control situation. Levels of von Willebrand factor antigen (VWF:Ag) and activity (VWF:RCo), factor (F) VIII, plasminogen activator inhibitor-1 (PAI-1), and clot-lysis time were slightly higher after levothyroxine 0.3 mg per day than after the control situation, but only levels of VWF were significantly increased compared to baseline values. After levothyroxine 0.45 or 0.6 mg per day, levels of fibrinogen increased by 17%, VWF antigen by 26%, VWF activity by 24%, factor VIII by 19%, factor IX by 14%, factor X by 7%, PAI-1 by 116%, clot-lysis time by 14%, and activated partial thromboplastin time decreased by 3%; all significant changes compared to after the control situation. We did not observe clear evidence of coagulation activation.
These findings suggest that thyroid hormone excess increases coagulation factor levels and inhibits fibrinolysis, in a dose-dependent fashion. This implies an increased risk of venous thrombosis during hyperthyroidism.

Chapter 5 concerns the unique case of a young woman who attempted suicide by auto-intoxication with 25 mg of levothyroxine. 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 support the data of Chapter 4 and indicate that thyroid hormone excess may not only lead to an increase in coagulation factor levels and inhibition of fibrinolysis, but also may enhance thrombin generation.

Chapter 6 investigates the effect of hyperthyroidism and hypothyroidism on thrombin-activatable fibrinolysis inhibitor (TAFI), a protein that links the coagulation and fibrinolytic system. The effect of hyperthyroidism on TAFI was studied in healthy volunteers who were treated with levothyroxine for 14 days. The effect of hypothyroidism on TAFI was studied in a multicentre observational cohort study. Blood was drawn before treatment of patients with newly diagnosed hyperthyroidism and when euthyroidism was achieved. Hyperthyroidism resulted in a hypofibrinolysis condition and enhanced TAFIa-dependent prolongation of clot-lysis, despite slightly decreased plasma TAFI levels. Hypothyroidism resulted in hyperfibrinolysis and a reduced TAFIa-dependent prolongation of clot-lysis. Alterations of TAFIa-dependent prolongation of clot-lysis in patients with thyroid disorders may cause an impaired haemostatic balance. The disturbed haemostatic balance in patients with hyperthyroidism might make them more prone for thrombosis, while the risk for bleeding may increase in patients with hypothyroidism.

Chapter 7 elaborates on whether the changes in factor VIII, von Willebrand factor, and fibrinogen as observed in patients with hypothyroidism are related to levels of thyroid hormone, or are at least partially mediated by thyroid stimulating hormone (TSH). In patients successfully treated for well-differentiated thyroid carcinoma, either levothyroxine was withdrawn (n=11) or recombinant TSH was administered (n=17) to stimulate thyroglobulin production. Blood was drawn before and after restart of levothyroxine (group 1) or in the days before and after administration of recombinant TSH (group 2). In group 1, the change from hypothyroidism to a slightly hyperthyroid state resulted in a rise in levels of factor VIII (+39.1 U/dL), von Willebrand factor (+32.0 U/dL), and fibrinogen (+9.6 g/L). In patients of group 2, in whom stable FT4 levels accompanied rising levels of TSH, no effect on coagulation parameters was observed. These findings suggest that the haemostatic abnormalities as observed in patients with thyroid disease are related to alterations in levels of free thyroxine rather than TSH.

Chapter 8 describes the results of a case-control study on leg vein thrombosis. Parameters of thyroid function were assessed in 190 cases with objectively confirmed venous thrombosis of the lower extremities (including deep venous thrombosis, calf vein thrombosis, and superficial thrombophlebitis) and 379 control subjects in whom leg vein thrombosis was objectively ruled out. Odds ratios (ORs) and 95% confidence intervals (CI) for the risk of venous thrombosis were estimated according to several cut-off levels derived from plasma levels observed in controls. We found the risk of venous thrombosis to gradually rise with increasing levels of free thyroxine (FT4). In the absence of traditional acquired risk factors, FT4 levels above 17 pmol/L, yielded a gender- and age-adjusted OR of 2.2 (95% 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 FT4 levels above reference range. These data suggest increasing levels of free thyroxine to be a risk factor for venous thrombosis and may have implications for both the prevention and management of this disease.

In Chapter 9, the association between increasing levels of free thyroxine and venous thrombosis is further explored using a large population-based case-control study of incident first venous thrombosis (the MEGA study). In contrast to the case-control design described in Chapter 8, blood samples were taken in the months following the thrombotic event. Thyroid function was assessed in 2177 cases and 2826 controls, and odds ratios (OR) with 95% confidence intervals (CI) were calculated. For cut-off levels, different percentiles of the values observed in the controls were used. We found an increased risk of venous thrombosis for higher levels of FT4, with odds ratios ranging from 1.5 (95% CI 1.2-1.8) for levels above the 90th percentile (19 pmol/L) to 2.2 (95% CI 1.0-4.7) for levels above the 99.5th percentile (23 pmol/L), relative to levels in the 25th to 75th percentile and adjusted for age, gender, and body mass index. The pattern of increasing risk with higher levels of FT4 was most pronounced for shorter time between thrombosis and blood sampling, and in men (OR 7.1; 95% CI 2.0-25.9 for levels above the 99th percentile). There was a similar association for low levels of TSH. No clear relation was found for antiTPO. These findings confirm that levels of FT4 are associated with an increased risk of venous thrombosis, in a dose-dependent fashion.

Chapter 10 describes the results of a nested case-control study that was conducted using the PHARMO Record Linkage System, a Dutch population-based pharmacy registry. In this study, the association between pulmonary embolism and the start of treatment for thyroid disease was investigated. Data on prescription use and hospitalisations of 3479 patients hospitalised for pulmonary embolism and 11830 gender- and age-matched controls without a history of pulmonary embolism were used. The date of hospitalisation was set as index date. New use of antithyroid agents or hospitalisation for thyrotoxicosis within 6 months after the index date (i.e. untreated hyperthyroidism at the index date) was significantly associated with pulmonary embolism (adjusted OR 3.22; 95% CI 1.12-9.22), whereas a relation between thyreomimetic agents and pulmonary embolism was observed for new use before the index date, especially within the first 3 months after treatment onset (adjusted OR 4.58; 95% CI 1.28-16.43). No association was found for new use of thyreomimetic agents after the index date or for new use of antithyroid agents before the index date. These findings suggest that both patients with untreated hyperthyroidism and patients who have recently started with thyreomimetic agents for hypothyroidism are at an increased risk for pulmonary embolism.

Chapter 11 systematically reviews the published evidence on the association between hypothyroidism and acquired von Willebrand’s syndrome. The MEDLINE and EMBASE databases were searched to identify all published clinical epidemiological and interventional
Part II: cortisol

Chapter 12 is a systematic review on the effects of endogenous hypercortisolism on coagulation and fibrinolysis as well as on the clinical outcome of venous thromboembolism. The MEDLINE and EMBASE databases were searched up to July 2008. The Newcastle-Ottawa Scale was used to assess study quality, and a scoring system divided studies into categories of low, medium, and high quality. Of 441 identified publications, 15 reports were included. They contained information on 8 cross-sectional, 2 intervention studies, and 8 cohort studies. No high-quality studies were identified. Hypercoagulability was suggested by high levels of factor VIII, IX, and von Willebrand factor and evidence of enhanced thrombin generation. A risk of 1.9% and 2.5% was reported for venous thromboembolism not provoked by surgery, whereas risk of postoperative venous thromboembolism varied between 0 and 5.6%, with one outlier of 20%. Venous thromboembolism was reported as cause of death in 0 to 1.9% of Cushing patients. Available studies suggest a high risk of venous thrombosis in patients with Cushing’s syndrome. Glucocorticoid-induced hypercoagulability as well as surgery and obesity almost certainly contribute to this thrombotic tendency.

Chapter 13 describes the results of a preliminary analysis of a retrospective multicentre cohort study on the incidence of venous thromboembolism in patients with Cushing’s syndrome, with special emphasis on the incidence prior to treatment onset and the risk of postoperative venous thromboembolism. A total of 298 patients with endogenous Cushing’s syndrome of benign origin, recruited from 5 academic medical centres in the Netherlands, were included; 240 with corticotropin-dependent and 58 with corticotropin-independent Cushing’s syndrome. Twenty-five patients experienced a venous thromboembolic event during the study period, resulting in an overall incidence of 15.4 (95% CI 9.4-21.4) per 1000 person-years. The incidence of venous thromboembolism prior to treatment was 170 (95% CI 8.5-25.5) per 1000 person-years (15 events). The risk of postoperative venous thromboembolism was 2.4% (95% CI 0.8-4.0%) (8 events in 338 surgeries); most events occurred between 1 week and 1 month after surgery. These findings indicate that patients with Cushing’s syndrome are at high risk of venous thromboembolism, especially during active disease and after surgery.

Chapter 14 aimed to systematically summarise the available evidence on the effects of glucocorticoid use on coagulation and fibrinolysis. MEDLINE and EMBASE databases were searched to identify published studies comparing glucocorticoid treatment with a glucocorticoid-free control situation. Subjects could be either patients or healthy volunteers. Results were expressed as standardised mean difference, if possible; data were pooled with a random-effects model. Of the 1967 identified publications, 36 papers were included. In healthy volunteers, a clear rise in factor VII, VIII, and XI activity was observed after glucocorticoid treatment, but these data alone provided insufficient evidence to support hypercoagulability. However, during active inflammation, glucocorticoids significantly increased levels of plasminogen activator inhibitor-1, whereas levels of von Willebrand factor and fibrinogen decreased. Peri-operative use of glucocorticoids inhibited the increase in tissue factor-plasminogen activator induced by surgery. This review showed differential effects of glucocorticoids depending on the clinical situation in which it is given. This is most likely due to their disease-modifying properties. Clinical outcome studies are needed to adequately assess the risk-benefit of glucocorticoid use per population when thrombotic complication is the focus.

Part III: Prolactin

Chapter 15 elaborates on the results of a case-control study in which the association between prolactin and venous thrombosis was investigated. Prolactin levels were assessed in 187 cases with objectively confirmed deep venous thrombosis (DVT), calf vein thrombosis, or superficial thrombophlebitis of the lower extremities and 374 control subjects in whom leg vein thrombosis was objectively ruled out. Median prolactin levels were higher in cases (6.7 µg/L) than in controls (5.6 µg/L). Odds ratios for the risk of venous thrombosis clearly increased with higher prolactin levels. For prolactin levels above the 75th percentile (8 µg/L), we found a gender-adjusted odds ratio of 1.7 (95% CI 1.1-2.7) as compared to levels below the 50th percentile (6 µg/L). This further increased up to an odds ratio of 4.7 (95% CI 1.9-11.7) for prolactin levels above the 97.5th percentile (16 µg/L). Adjustment for potential confounders slightly reduced the odds ratios. The risk was most pronounced in pre-menopausal women. No clear association was observed for men or post-menopausal women. These data suggest that higher prolactin levels, even within the physiological range, are associated with venous thrombosis. Future studies are needed to evaluate the causality of this relation.

Finally, Chapter 16 aimed to explore the relationship between prolactin, acute stress, and inflammation in patients with myocardial infarction. We hypothesised that prolactin levels may only temporarily be increased in patients with myocardial infarction, as a result of either the acute neuroendocrine stress response or the systemic inflammatory response. A case-control study was performed among 40 patients with myocardial infarction and 39 controls. Prolactin levels at inclusion did not differ between cases and controls (7.0 ng/mL and 6.0 ng/mL, respectively, p=0.28). Two to three weeks later prolactin levels in cases had not decreased. However, univariate regression analysis indicated that hsCRP is associated with prolactin levels (regression coefficient β 0.11; 95% CI 0.01-0.21) in cases during the acute phase of myocardial infarction. These findings indicate that prolactin is involved in the systemic inflammatory response which takes place during myocardial infarction, however, this association is not strong enough to induce higher prolactin levels in patients with myocardial infarction.