Hormones, haemostasis, and the risk of thrombosis
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Chapter 1

General introduction and outline of the thesis

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GENERAL INTRODUCTION

Venous thrombosis is characterised by obstructive clot formation, occurring in one or more of the blood vessels that carry blood back to the heart. Impeded venous blood flow in a leg or other part of the body is generally not a direct danger to vital functions. However, the clot may dislodge and cause a pulmonary embolism, which is potentially life threatening. In general, venous thrombosis occurs in the event of an imbalance in the haemostatic system, the complex and subtle process that is essential for the integrity of our vasculature. In case of damage to a blood vessel, platelets adhere to subendothelial collagen and aggregate to form a platelet plug. Simultaneously, the exposed collagen and tissue factor activate the coagulation cascade that ends in the formation of fibrin strands. The fibrin network then stabilises the blood clot. This series of events is modulated by both anticoagulant proteins and the fibrinolytic system to prevent us from pathological thrombus formation. However, when these processes stop to act in concert, the risk of excessive thrombus formation is increased.

Several genetic and acquired factors have been found to affect the haemostatic balance and thereby increase the risk of venous thrombosis. These risk factors include thrombophilia, surgery, trauma, cancer, pregnancy and puerperium, but also the use of oral contraceptive agents or hormone replacement therapy. The ability of oral contraceptive agents or hormone replacement therapy to precipitate venous thrombosis is thought to be related to their content of the female hormones oestrogen and progesterone. Hormones exert their action by binding to a tissue-specific receptor. Although the type of receptor and the associated intracellular pathways may differ between the classes of hormones, certain general principles apply to hormone-receptor interactions. The hormone-receptor complex almost invariably acts to increase or decrease gene transcription. Through this mechanism, hormones may alter protein synthesis in various tissues, including coagulation and fibrinolytic protein synthesis at the hepatic and endothelial level. Other elements of the haemostatic system may be influenced as well, such as platelet activation and aggregation, blood flow, or the function of the vascular wall, and it is therefore a logical consequence that hormones may be involved in the pathogenesis of venous thrombosis. In fact, the hypothesis of an association between hormones, haemostasis and venous thrombosis has existed for quite some time. Thyroid hormones, haemostasis and venous thrombosis have existed for quite some time. Thyroid hormones have been associated with venous thrombosis, and it is logical to conclude that hormones may be involved in the pathogenesis of venous thrombosis. In fact, the hypothesis of an association between hormones, haemostasis and venous thrombosis has existed for quite some time.

The thesis consists of three parts involving the role of thyroid hormone, cortisol, and prolactin.

Chapter 2 reviews the available literature on the effects of pituitary, adrenal, and parathyroid hormones on haemostasis and thrombosis. In Chapter 3, the contribution of thyroid hormone, cortisol, the somatotropic hormones, and prolactin in the development of cardiovascular disease, and atherothrombosis specifically, is discussed.

The first part of the thesis addresses the effects of thyroid hormone. We assessed the overall effect of thyroid hormone on coagulation and fibrinolysis in a crossover study in healthy volunteers, who were randomised to receive either levothyroxine (synthetic thyroid hormone) or no medication. The results of this study are presented in Chapter 4. In Chapter 5, we describe the case of a young woman who attempted suicide by levothyroxine intoxication, which presented the unique situation of assessing the haemostatic effects of severe thyroid hormone excess. Chapter 6 concerns the effects of hyperthyroidism and hypothyroidism on thrombin-activatable fibrinolysis inhibitor, a protein that links the coagulation and fibrinolytic systems. Whether the haemostatic abnormalities as observed in thyroid dysfunction are solely the result of alterations in thyroid hormone levels or may be influenced by thyroid stimulating hormone as well, is discussed in Chapter 7. In Chapter 8 and Chapter 9, the risk of venous thrombosis associated with different levels of thyroid hormone was assessed by using two separate case-control studies. Chapter 10 aims to evaluate the risk of venous thrombosis associated with thyroid dysfunction, while at the same time analysing the effects of corrective treatment. Finally, the relation between thyroid hormone deficiency, haemostasis, and overt bleeding was assessed by systematically reviewing the available evidence in Chapter 11.

The second part of this thesis concerns the effects of cortisol, a glucocorticoid hormone. In Chapter 12, the available evidence on the effects of endogenous glucocorticoid excess, as observed in patients with Cushing’s syndrome, was systematically reviewed. Outcome measures were parameters of coagulation and fibrinolysis, and the occurrence of venous thrombosis. Chapter 13 describes the preliminary findings of a large retrospective multicentre cohort study on the overall incidence of venous thrombosis in patients with Cushing’s syndrome, with special emphasis on the three years prior to the start of treatment and the postoperative period. Glucocorticoids are often administered in a high dose to patients with inflammatory diseases. In Chapter 14, the published studies on the effects of glucocorticoid use on haemostasis were systematically reviewed and critically appraised.

The third part of this thesis addresses the stress-hormone prolactin. In Chapter 15, the association between increasing levels of prolactin and venous thrombosis was assessed in a case-control design. Whether there is a relation between prolactin, acute stress, and inflammation in patients with myocardial infarction is described in Chapter 16.