Endocrine determinants of haemostasis and thrombosis risk: Focus on thyroid hormone
Elbers, Laura

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General Introduction and Outline of the Thesis
GENERAL INTRODUCTION

In June 1905, Ernest Starling (1866-1927) first used the word ‘hormone’ which was derived from the Greek word ‘ormao’ meaning ‘to arouse or excite’ (1). Hormones were defined as ‘the chemical messengers which, speeding from cell to cell along the blood stream, may coordinate the activities and growth of different parts of the body’. During the subsequent 100 years, the knowledge on hormones has expanded widely and this led to various therapeutic options for various diseases (2). Hormones exert their action by binding to tissue-specific receptors. The hormone-receptor complex then increases or decreases gene transcription. By this mechanism, hormones may alter protein synthesis in various tissues. In this thesis we aimed to explore the hormonal influence on the haemostatic system and its potential clinical consequences.

Haemostasis is the process that maintains the integrity of a closed circulatory system after vascular damage (3). Primary haemostasis is defined as the formation of the primary platelet plug. Secondary haemostasis is the process of fibrin formation to stabilize the platelet plug. The process of dissolution of fibrin in blood clots is called fibrinolysis. These physiological processes may be unbalanced which results in pathology, e.g., arterial or venous thrombosis. The most common presentations of venous thrombosis are deep vein thrombosis of the lower extremity and pulmonary embolism which can be life-threatening. Myocardial infarction and ischemic stroke are the most common presentations of arterial thrombosis.

Hormones may influence the risk of both arterial and venous thrombosis via different mechanisms. The effect on arterial thrombosis is mainly indirect. For instance, thyroid hormone stimulates the clearance of cholesterol in the liver (4). The risk of venous thrombosis is altered via an influence on primary and secondary haemostasis. Thyroid hormone influences coagulation and fibrinolytic activity by increasing or decreasing gene transcription at the level of the liver and endothelium (5, 6).

Venous thrombosis is considered as a multi-factorial disease in which multiple genetic and environmental determinants combine to cross a so-called ‘thrombotic threshold’ (7). The first discovered hormonal risk factor for the development of
venous thrombosis was the use of oral contraceptives (8, 9). The link between hyperthyroidism and venous thrombosis was initially noted in a series of case reports (10, 11). Ever since, several larger studies have indicated that hyperthyroidism is associated with a variety of changes in haemostatic factors, together resulting in a hypercoagulable state (12, 13). Other studies have shown that patients with hyperthyroidism may have an increased risk of developing venous thrombosis (14-16).

The knowledge on the effect of hyperthyroidism on thrombosis risk and its clinical relevance is expanding, also among clinicians. Hyperthyroidism is a treatable risk factor for venous thrombosis with an estimated incidence of 51 per 100,000 per year and a prevalence of 1.72% in Europe (17). Considering hyperthyroidism as a risk factor for venous thrombosis could diminish the need for prolonged anticoagulant therapy. The precise mechanism by which thyroid hormone influences the haemostatic system remains to be elucidated. This is relevant in the light of the current development of thyroid hormone receptor β (TRβ) specific thyreomimetics with very limited uptake in non-hepatic tissues to lower low-density lipoprotein cholesterol, as TRβ is expressed in the liver where coagulation factors are synthesized. The hypothesis that these compounds could induce a hypercoagulable state has been addressed only once but no clear conclusions could be drawn (18). On the other side of the spectrum, hypothyroidism has been associated with a hypocoagulable and hyperfibrinolytic state (19, 20) which translates into a bleeding tendency (21). In line with this concept, one recent study suggested that, low levels of free thyroxine, even within the reference range, lead to a higher bleeding risk (22).

In addition to thyroid hormone, other hormones have also been reported to influence the haemostatic system in a clinically relevant way. An increased risk of venous thrombosis during glucocorticoid excess, whether endogenous e.g. by Cushing’s syndrome or exogenous by glucocorticoid use, has previously been reported (23-25). The contribution of genetic glucocorticoid receptor variants, representing different cortisol sensitivities, has been reported with regard to the risk of cardiovascular disease (26). The effect of genetically determined altered cortisol sensitivity on the risk of venous thrombosis has not been investigated before.

Data regarding the effects of the anterior pituitary hormone prolactin on platelet activity and haemostatic mechanisms are conflicting. Although a significant
proportion of the current data suggests that hyperprolactinaemia is associated with hypercoagulability and increased thromboembolic risk, further studies are required to support this hypothesis (27, 28). A physiological condition leading to major endocrine changes, including elevated prolactin, is pregnancy. Pregnancy is also associated with marked alterations in the proteins of the coagulation and fibrinolytic systems, which are, at least partially, caused by increased levels of progesterone and estrogens (29, 30). The net effect of these pregnancy-induced changes is to produce a hypercoagulable state that prevents excessive blood loss during delivery. As a consequence, the risk of venous thrombosis is markedly increased during pregnancy and puerperium, representing one of the leading causes of maternal death (31). The exact underlying mechanism is not yet elucidated and the role of prolactin has only been scarcely investigated. In particular, it is not fully understood why the risk of venous thrombosis during the postpartum period is even 5 times higher than during pregnancy (32).

For several additional hormones such as parathyroid hormone and aldosterone, a possible effect on the haemostatic system has only been carefully suggested. Only a few studies with several methodological limitations have been performed (28). Thus, the field of effects of hormones on haemostasis and the clinical relevance of this association is still to be further explored. This thesis aims to bring further insights into the intriguing link between the hormonal and haemostatic system. By focussing on several hormones, we aimed to unravel both the underlying mechanisms by which these hormones affect the haemostatic system as well as the risk of clinical thrombotic manifestations.

**OUTLINE OF THIS THESIS**

This thesis consists of 3 parts. In the first part, we study the effects of thyroid hormone on the haemostatic system. In Chapter 2 we review the current knowledge on the influence of thyroid hormone on the haemostatic system and the risk of venous thrombosis and bleeding episodes. Chapter 3 is our first attempt to elucidate the mechanism by which hyperthyroidism leads to a hypercoagulable state.
We studied changes in expression of inflammation-related genes of the leukocyte RNA expression profile in healthy subjects in response to supraphysiological doses of levothyroxine. In Chapter 4, we tested the hypothesis that the hypercoagulable state in hyperthyroidism is mediated via the thyroid hormone receptor β using a unique cohort of patients with resistance to thyroid hormone due to a thyroid hormone receptor β mutation. In Chapter 5, we hypothesized that low levels of preoperative free thyroxine are associated with an increased risk of major bleeding during and after bariatric surgery.

The second part of this thesis concerns the effect of thyroid hormone on lipids and lipoproteins. The well-known association between thyroid hormone status and plasma levels of low-density lipoprotein (LDL) cholesterol led to the development of thyroid hormone mimetics as lipid-lowering agents. However, until now, none of the thyromimetics reached the stage of completing a phase III clinical trial without deleterious side effects. In Chapter 6 we review the currently available literature on thyromimetics investigated for the treatment of dyslipidemia and the challenges for the development of novel agents. Eprotirome, a TRβ selective thyroid hormone analogue with very limited uptake in non-hepatic tissues, was recently shown to induce significant increases in markers of liver injury along with a modest decrease in atherogenic lipids and lipoproteins (33). To achieve more insight into whether these effects on liver parameters were compound specific or the effect of mimicking hepatic thyrotoxicosis, we studied the effects of supra-physiological levothyroxine dosages on liver parameters, plasma lipids and lipoproteins in Chapter 7.

The final part of this thesis addresses several other hormones. In Chapter 8 we questioned whether haplotypes of the glucocorticoid receptor gene with different cortisol sensitivities are associated with an increased risk of venous thrombosis. In Chapter 9 we investigated the association between prolactin and markers of coagulation and fibrinolysis in healthy pregnant women. To achieve more insight into the etiology of the increased risk of venous thrombosis in the postpartum period, in Chapter 10 we questioned whether the left-predominance of deep venous thrombosis during pregnancy, is also present during the postpartum period. Abnormal coagulation tests have been observed in patients with primary hyperparathyroidism suggesting a prothrombotic effect of parathyroid hormone. The aim of
Chapter 11 was to investigate the influence of hyperparathyroidism secondary to moderate-severe vitamin D deficiency on the coagulation and fibrinolysis system. Aldosterone seems to influence the haemostatic system by several mechanisms and to increase the risk of thrombosis. In line, recent literature suggested that the use of spironolactone leads to more bleeding events. Therefore, our objective was to assess the impact of aldosterone suppression due to the use of mineralocorticoid receptor antagonists on venous and arterial thrombosis, bleeding events and mortality. In Chapter 12 we describe our systematic review and meta-analysis of randomized controlled trials on mineralocorticoid receptor antagonists in patients with conditions that are associated with secondary hyperaldosteronism.
REFERENCE LIST