Thyroid disease and haemostasis: a relationship with clinical implications?
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Chapter 1

General Introduction and Outline of the Thesis

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**General introduction**

Haemostasis is a well-balanced system that prevents us from bleeding without inducing thrombotic events. The complex regulation of haemostasis is very similar to a 'symphony orchestra', in which coagulation and fibrinolytic system interact simultaneously 'in concert' with cellular surfaces of platelets and the vascular endothelium[1]. The endothelium plays a crucial role in maintaining the blood in a fluid state. Its surface has several anticoagulant properties: when there is a breech in the integrity of the vessel wall platelets adhere to subendothelial collagen and clot formation is initiated. Subsequently, platelets aggregate and fibrin strands are formed while anticoagulant proteins and the fibrinolytic system regulate and limit this clot formation[2].

It is a spontaneous thought to believe that hormones, which exert their effects in all tissues and organs, interfere with the haemostatic balance. Apart the well-known interactions with sex hormones, oral contraceptives and hormonal replacement therapy, almost all hormones have been described to directly influence both primary and secondary haemostasis[3-4]. A wide variety of endocrine disorders have been associated with both mild abnormalities in laboratory coagulation tests, and clinical thrombotic or bleeding manifestations[6]. Among them, the first description of an interaction was with thyroid disorders, when both Kaliebe and Doyle reported an episode of cerebral vein thrombosis in a thyrotoxic patient in 1913 and 1927, respectively[5]. Several elements of the process of thrombus formation may be involved[6-7]. Both thyroid dysfunction and autoimmunity may modify physiological processes of primary and secondary hemostasis and lead to bleeding or thrombosis. Idiopathic thrombocytopenic purpura, secondary antiphospholipid syndrome, or acquired haemophilia have been associated in individual cases with autoimmune thyroid disorders[8]. Thyroid hormones influence the coagulation and fibrinolytic system mainly by the interaction between the hormone and its receptors[9]. Various abnormalities have been described, ranging from subclinical laboratory abnormalities to patients with major haemorrhages or fatal thromboembolic events[7].

However, in clinical practice the relationship between thyroid hormones and the coagulation system is often ignored. One of the reasons could be that, although several in vivo abnormalities have been reported in patients with hypothyroidism and hyperthyroidism, most published studies focus on laboratory measurements, and good studies on the relationship between thyroid dysfunction and clinically manifest bleeding or thrombosis are lacking. In addition, most previous studies have important methodological drawbacks, such as lack of a control group, small study size, heterogeneity of cause and severity of thyroid dysfunction, and different laboratory assays.

The limited evidence has stimulated us to start a research program to improve the knowledge on the relationship between endocrine disorders and haemostasis, starting from thyroid dysfunctions. To understand both the scientific and clinical relevance of this relationship, it is important to stress that both cardiovascular disease and venous thromboembolism are multi-causal diseases in which usually more than one genetic or environmental condition coincides to produce clinically apparent thrombosis[10]. For this reason, also weak thromboembolic risk factors may be clinical relevant, especially if treatable such as endocrine disorders.
OUTLINE OF THE THESIS

The thesis starts with an overview of the literature. Chapter 2, 3, 4 and 5 were performed with the purpose to generate well-founded hypotheses and to give direction for future basic and clinical research on this topic. Chapter 2 is a brief overview of the literature on the relationship between endocrine disorders and haemostasis. In Chapter 3 we systematically review the studies on the effects of thyroid dysfunction on coagulation and fibrinolysis, while in Chapter 4 the current evidence on relationship between hypothyroidism and acquired von Willebrand syndrome is reviewed. In Chapter 5 we give an overview of the literature on thyroid disease and cerebrovascular disease.

In Chapter 6 the results of a pilot study on the presence of overt and subclinical thyroid disorders in patients with venous thrombosis are described. We subsequently measured thyroid hormone concentrations and antibodies in a larger group of patients with venous thrombosis and control persons (Chapter 7). In addition, in a large database in which hospital admission for pulmonary embolism and the use of medication was registered we analysed whether treatment for thyroid disorders was associated with pulmonary embolism (Chapter 8). The effect of hyperthyroidism on coagulation and fibrinolysis markers is described in a randomized controlled crossover trial in healthy volunteers in Chapter 9 and, in particular, the effect of hypothyroidism and hyperthyroidism on thrombin-activatable fibrinolysis inhibitor in Chapter 10. A young woman who attempted suicide and took a very high dose levothyroxine gave us the opportunity to study the effect of this on coagulation and fibrinolysis (Chapter 11).

The second part of the thesis is dedicated to the interactions of thyroid disease with vitamin K antagonist. Chapter 12 is an editorial in which we commented the available evidence and highlighted the lack of published studies, in particular on subclinical hyper- and hypothyroidism. In two small pilot studies, Chapter 13 and 14, we tested the effect of subclinical hypothyroidism on vitamin K antagonist stability and sensitivity and the effect of thyroid auto-antibodies on vitamin K warfarin stability. In Chapter 15 we describe a patient with hyperthyroidism and recurrent deep venous thrombosis during optimal anticoagulation. Chapter 11 and 15 are case reports from the Netherlands and Italy, respectively. Besides to support the clinical relevance of the relationship between thyroid disease and haemostasis, these chapters reinforce and ‘definitely demonstrate’ that the scientific relationship of our two countries can help ‘the haemostatic orchestra’ playing ad libitum.
References