The close relationship between thyroid hormones and the coagulation system has been known since the beginning of the past century and has been analysed over the decades by several investigators (1). Accordingly, various haemostatic abnormalities, involving both primary haemostasis and the coagulation/fibrinolytic system, have been reported in patients affected by a wide variety of endocrine disorders and range from subclinical laboratory abnormalities to clinically relevant haemorrhagic or thrombotic events (2-5). In particular, several studies have investigated the in vivo effect of overt and subclinical thyroid dysfunction on blood coagulation and fibrinolytic factors, suggesting that a procoagulant state is present in both overt and subclinical hyperthyroidism and in subclinical hypothyroidism (increased plasma levels of fibrinogen, von Willebrand factor [VWF], factors VII-X and plasminogen activator inhibitor-1 [PAI-1]), while a bleeding tendency is observed in overt hypothyroidism (reduced plasma levels of VWF, factors VII-XII, PAI-1 and α2-antiplasmin) (3, 6-9).

A number of pathogenic mechanisms have been suggested to explain these relationships, including the effects of thyroid hormones on the synthesis of coagulation factors or thyroid-related autoimmune processes, also involving the haemostatic system. Although several hypotheses have been proposed, the exact underlying pathogenic mechanisms have not yet been elucidated and are still under investigation (10). In this context the three studies published in this and recent issues of Thrombosis and Haemostasis shed further light on the complex interaction between the thyroid and haemostasis.

In the first study, Krysiak et al. prospectively investigated the haemostatic changes and response to levothyroxine and selenomethionine in 155 euthyroid patients with Hashimoto’s thyroiditis (11). The 149 patients who completed the study were randomised to six months of treatment with levothyroxine and selenomethionine, alone or in combination, or placebo. All parameters analysed (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen, factor VII, VWF, factor X and PAI-1) were abnormal at baseline and partially or completely corrected after treatment with levothyroxine and selenomethionine. The findings of this study are very interesting as they document for the first time that haemostatic disturbances may be present in patients with Hashimoto’s thyroiditis, the most common thyroid disorder, independently of their thyroid hormone status and, most importantly, that they were reversed by treatment. Thus, while these results suggest that atherosclerosis may develop even at an early stage of chronic thyroiditis (i.e. without hypothyroidism), they also raise the question of when (and with which drugs) to start treatment in such patients to reduce their vascular risk.

The role of the thrombin-activatable fibrinolysis inhibitor (TAFI), which represents a link between the coagulation and fibrinolytic systems, was explored in the second study, conducted by Verkleij et al. (12). To evaluate the effect of hyperthyroxinaemia on TAFI levels, two single-blinded, crossover trials were conducted in 26 healthy volunteers who were randomised to receive levothyroxine or no medication for 14 days, whereas the effect of hypothyroidism on TAFI was studied in a multicentre, observational cohort study involving 20 patients. The authors found a hyperfibrinolytic condition with an enhanced, activated TAFI-dependent prolongation of clot lysis during thyroid hormone excess, whereas hypothyroidism resulted in hyperfibrinolysis and a reduced activated TAFI-dependent prolongation of clot lysis. The findings of this study are also very intriguing as they provide novel and important information on the pathogenic mechanisms underlying the clinical evidence of an increased bleeding tendency associated with hypothyroidism and an enhanced thrombotic risk in patients with thyroid hormone excess.

Hyperthyroidism-associated haemostatic changes were also analysed in the third study, a systematic review and meta-analysis conducted by Stuijver et al. (13). After a search of MEDLINE, PUBMED and reference lists, the authors included in their analysis 29 articles, consisting of 51 observational or experimental studies. Their meta-analysis showed that both subclinical and overt hyperthyroidism were accompanied by increases in factor VIII, factor IX, VWF, fibrinogen and PAI-1 thus shifting the haemostatic balance towards a hypercoagulable and hypofibrinolytic state. Thus, the pooled-analysis of the literature results provided consistent evidence that patients with thyrotoxicosis are at increased risk of developing venous thrombosis (14), although prospective studies are necessary to further define the clinical relevance of this association and the possible impact of pharmacological treatment of the hormonal dysfunction on coagulation-fibrinolytic abnormalities. Studies should also be conducted to evaluate the role of concomitant inherited or acquired thrombotic risk factors in triggering venous thrombosis and the safety and effectiveness of thromboprophylactic measures in high-risk hyperthyroid patients.
Thus, all three studies supply important pieces towards the completion of the complex puzzle that is the thyroid-haemostasis interaction. Nonetheless, important aspects of comorbidities associated with thyroid disease need to be considered. For example, thyroid disease has been associated with atrial fibrillation, and this common arrhythmia has been associated with an increased risk of thromboembolism, and part of the holistic management of atrial fibrillation (AF) requires full assessment of all comorbidities (15). This is highly relevant, given that adequate thromboprophylaxis can markedly reduce the burden of stroke in AF (16-18). In addition, thyroid disease can be associated with cardiac dysfunction, with a cardiomyopathy. Given that heart failure can be associated with a significant risk of thromboembolism, which is another important consideration (19). Clearly, thyroid disease is part of a systemic condition, and the associated prothrombotic state (as reflected by the abnormalities of haemostatic and fibrinolytic markers) would enhance the associated risks of thromboembolism.

**Conflicts of interest**

None declared.

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**References**