Thyroid, hemostasis and thrombosis

F. Marongiu\textsuperscript{1}, C. Cauli\textsuperscript{1}, and S. Mariotti\textsuperscript{2}

\textsuperscript{1}Chair of Internal Medicine, \textsuperscript{2}Chair of Endocrinology, Policlinico Universitario di Monseratto, University of Cagliari, Cagliari, Italy

ABSTRACT. The aim of this paper is to briefly review some practical aspects of the relationship between thyroid function and several disorders of the hemostatic system in terms of bleeding and thrombosis. Thrombocytopenia, acquired hemophilia, hypercoagulability, cardioembolism and other biochemical coagulative and fibrinolytic abnormalities have been described in the past years both in hyper- and hypothyroidism. Since most of hyper- and hypothyroid conditions are the consequence of autoimmune thyroid disease (1), either deranged immune function, altered circulating thyroid hormone concentration, or both may concur in the pathogenesis of hemostatic disorders of potential crucial clinical impact. These aspects will be outlined and discussed in an attempt to give answers to some questions, often arising in the clinical approach. (J. Endocrinol. Invest. 27: 1065-1071, 2004) ©2004, Editrice Kurtis

THYROID AND BLEEDING DISORDERS

Both thyroid function and autoimmunity may concur in the pathogenesis of bleeding disorders that may occasionally be observed in thyroid diseases. In hyperthyroidism due to toxic diffuse and multinodular goiter platelet count and volume may be respectively decreased and increased, but these findings are usually devoid of clinical relevance (2). An increased platelet turnover induced by excess of thyroid hormones may explain these abnormalities (3-5). A mild bleeding tendency has been described in hypothyroidism, due to platelet abnormalities, low levels of von Willebrand factor (vWF) and other blood coagulation factors, and to increased fibrinolytic activity (6,7). Moreover, an acquired von Willebrand syndrome may complicate the course of hypothyroidism and can be reversed by treatment with L-T\textsubscript{4} (8). Nevertheless, the fibrinolytic activity has been found to be different in patients with various degrees of hypothyroidism. In fact, patients with severe hypothyroidism showed an enhanced fibrinolytic activity, expressed by higher levels of d-dimers concomitantly with a lower activity in \( \alpha_2 \)-antiplasmin and plasminogen activator inhibitor.

In contrast, patients with moderate hypothyroidism exhibited an inverse behavior of these parameters, which can be interpreted as lower fibrin dissolution ability (9). These findings indicate that different alterations of fibrinolytic activity are observed in various degrees of thyroid failure and suggest that moderate hypothyroidism is associated with an excess of fibrin deposition.

Immunological mechanisms may be responsible for important bleeding disorders in thyroid diseases. In fact, idiopathic thrombocytopenic purpura (ITP) may be associated to autoimmune thyroid disease in the context of autoimmune polyendocrinopathies (10). This association is more frequently observed in Graves’ disease (11) and familial forms of this association have been described (12). ITP is an autoimmune disorder (13) in which platelets with antibodies on their surface are removed by macrophages in the reticuloendothelial system at times leading to severe thrombocytopenia. When ITP complicates the course of Graves’ disease, a complete remission can be achieved after restoration of the euthyroid state (11): thus, from a practical point of view, patients should not be treated with corticosteroids or immunoglobulins until the platelet count remains above 30 x 10\textsuperscript{9}/l. On the other hand, it should be recalled that autoantibodies against thyroglobulin and thyroid microsomal/peroxidase antigen can be found in patients with ITP in a significant percentage, such as 8-14 and 17-41%, respectively (14). These antibodies should therefore be measured in patients with ITP.
in order to detect frequently associated subclinical autoimmune thyroid dysfunctions. A much more unusual condition associated with thyroid autoimmunity is acquired hemophilia, characterized by autoantibodies against factor VIII. Only two cases have been reported to date (15, 16). Both patients showed severe bleeding: one was treated with L-T₄ for Hashimoto’s thyroiditis which evolved in Graves’ disease, while the other was found to suffer from a pathetic hyperthyroidism. Acquired hemophilia shows overt bleeding together with a prolongation of the activated partial thromboplastin time (APTT) which is not corrected by addition of 50% normal plasma. This very simple test should therefore be taken into account if prolonged in a patient with bleeding tendency and autoimmune hyperthyroidism.

**THYROID AND THROMBOSIS**

*Hyperthyroidism and thrombosis*

*Does a hypercoagulable state exist in hyperthyroidism?*

Several coagulative proteins such as fibrinogen (17), factor IX (18) and factor VIII (19, 20) have been found to be increased in hyperthyroidism. These findings have been interpreted as an expression of an acute phase reaction together with an enhanced protein synthetic activity, typical of thyrotoxicosis. However, hyperfunctioning thyroid gland per se seems to produce large amounts of tissue factor, the major trigger of blood coagulation (21). This was indirectly confirmed when blood coagulation activity was studied in patients with autoimmune hyperthyroidism, in whom thrombin activity, which normally activates fibrinogen to fibrin, was found increased on measuring plasma fibrinopeptide A levels, a sensitive indicator of thrombin activity in vivo (22). In the same study (22), increased levels of Bβ 15-42 peptide, a sensitive indicator of plasmin activity, were concomitantly found. It is conceivable that the activation of fibrinolysis by plasmin is a phenomenon secondary to fibrin formation, to balance fibrin deposition with fibrin dissolution (Fig. 1). Nevertheless, interactions between thyroid hormones and the hemostatic system pass through the endothelial system, therefore the puzzle becomes more complex. Proteins which are thought to be indicators of endothelial damage (23), such as thrombomodulin (TM) and vW, have been studied during hyperthyroidism. TM is an endothelial cell surface glycoprotein that plays a crucial role in neutralizing thrombin while forming a complex TM-thrombin. The latter activates protein C, which regulates thrombin production by deactivating factors V and VIII (24). vW acts as a bridge glycoprotein between sub-endothelial collagen and platelets in the early phase of the hemostatic plug. It is synthesized in the endothelial cells and stored and released from granules called Weibel-Palade bodies (25). TM serum levels have been found to be strongly correlated to serum levels of thyroid hormones (26). Both TM and vW increased significantly in hyperthyroid patients (27). Taken together, these findings indicate that thyroid hormones exert a peripheral activity affecting the endothelial function and possibly inducing a shift from the physiological endothelial anti-thrombotic properties to a procoagulant status. Besides the effects of circulating thyroid hormones, a hypercoagulable status could also be related to immunological abnormalities in autoimmune hyperthyroidism (Graves’ diseases). In keeping with this concept, fibrinopeptide A did not decrease when

![Diagram](image_url)

Fig. 1 - The events that lead to fibrin deposition and dissolution are summarized. Fibrin as well as fibrin monomer are in turn attacked by fibrinolysis which, by means of plasmin, removes Bβ 15-42 from fibrin monomer and fibrin, and D-dimer only from definitive fibrin. In the figure the products of coagulation activity are also represented: prothrombin fragment 1+2 (F1+2) and fibrinopeptide A (FPA), which are released by the action of factor Xa and thrombin from prothrombin and fibrinogen, respectively.