Coagulation disorders in thyroid diseases

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Introduction

Various abnormalities of coagulation occur in patients with thyroid diseases, and may range from subclinical laboratory abnormalities to clinically significant disturbances of coagulation and, rarely, major hemorrhage or thromboembolism (1). Patients with hypothyroidism are at particular risk of hemorrhage (2). In contrast, patients with hyperthyroidism display a tendency to develop thromboembolic complications, with major embolism accounting for up to 18% of deaths in patients dying from thyrotoxicosis (3). Pathogenesis of coagulopathies associated with thyroid diseases may include direct and indirect effects of excess or deficiency of thyroid hormones on platelet maturation and function, on synthesis and action of coagulation factors, and on altered blood viscosity (4). In addition, coagulopathies in patients with autoimmune thyroid diseases may be related to an individual’s underlying susceptibility to develop autoimmune diseases. In this review, we will summarize the spectrum of coagulation disorders associated with thyroid diseases, discuss recent progress in the understanding of their pathogenesis, and provide clinical guidelines for their management.

Abnormalities of coagulation in hyperthyroidism

Owing to the pleiotropic actions of thyroid hormones, various abnormalities of coagulation parameters may occur in the clinical setting of hyperthyroidism, some of which deserve particular attention (Table 1). Patients with hyperthyroidism may exhibit accelerated platelet turnover, shortened platelet survival and, consequently, mildly reduced peripheral platelet counts, the latter usually being subclinical (5–7). Based on studies in humans and animal models, increased platelet destruction by an activated reticuloendothelial system has been attributed a pivotal role in the increased platelet turnover associated with hyperthyroidism (6, 8). In hyperthyroid patients, enhanced platelet turnover persisted even after a euthyroid state had been restored for three months or less using antithyroid drugs. By contrast, platelet survival returned to normal in patients who had been kept euthyroid for more than six months. Furthermore, administration of tri-iodothyronine to euthyroid rats resulted in an increased sequestration capacity of the reticuloendothelial system with enhanced clearance of platelets and heat-damaged red blood cells (8). In addition, patients with hyperthyroidism displayed a higher mean platelet volume of 9.2 fl (normal range: 5.8–8.4 fl) as compared with 7.9 fl after a euthyroid state had been achieved, possibly reflecting recruitment of younger, partially immature platelets from the bone marrow (9). All of these platelet abnormalities are completely reversible once a euthyroid state has been achieved (7, 9).

Despite these platelet changes, patients with hyperthyroidism are at particular risk of developing major thromboembolic complications associated with high mortality (3). Various factors may contribute to the hypercoagulable state associated with hyperthyroidism, including increased blood volume (mediated by increased erythropoietin production in response to elevated oxygen requirements), elevated hepatic protein synthesis, and enhanced thrombin and plasmin activity, as well as excessive fluid loss resulting from increased metabolic and respiratory rate, and sweating (4). In addition, atrial fibrillation, which occurs in 5–40% of patients with hyperthyroidism, represents an important risk factor of cardiogenic thromboembolic disease (10–12). To date, limited recommendations exist to guide the management of hyperthyroid individuals who present with atrial fibrillation (10, 12). The efficacy and safety of warfarin has not been prospectively studied in patients with hyperthyroidism-related atrial fibrillation. Thus, current recommendations are based on guidelines developed for the subgroup of euthyroid patients with nonvalvular atrial fibrillation (12–15). Administration of warfarin may be indicated in patients with persistent hyperthyroidism-related atrial fibrillation who are older than 60 years, and who present with heart failure and organic heart disease, especially when combined with an enlarged left atrium (14, 15). By contrast, acute atrial fibrillation in younger patients without underlying heart disease does not usually necessitate administration of warfarin (12, 14, 15). No data have yet become available regarding usage of aspirin as an alternative anticoagulant under these circumstances.
Autoimmune thyroid diseases and thrombocytopenic purpura

Autoimmune thrombocytopenic purpura (AITP) results from decreased survival of platelets due to immune-mediated, peripheral destruction of sensitized platelets in the reticuloendothelial system (16, 17). In patients with AITP, elevated thyroglobulin and microsomal antibodies are detected in 8–14% and 17–41% of patients respectively, in the absence of clinical thyroid disease (18). Although infrequent, the association of AITP and Graves’ disease is well established (for review see references (19–21)). Follow-up studies in patients with AITP indicated that hyperthyroidism developed in 8–14% of patients (19, 20). Conversely, easy bruising, thrombocytopenia (<150 000/µl), and elevated levels of platelet-bound IgG, signs and symptoms of AITP, were detected in 11 of 22 patients with Graves’ disease (22). Both Graves’ disease and AITP are characterized by abnormal B cell function. B cell clonal expansion and aberrant production of antibodies directed against platelet glycoproteins and the thyrotropin receptor (TSH-R) respectively (20, 23). Additional features common to Graves’ disease and AITP include female predominance, peak incidence between 30 and 50 years of age, and responsiveness to various forms of immunosuppressive therapy (17, 24–26). Further, Graves’ disease and AITP may coincide with malignancy (27) or other autoimmune diseases such as myasthenia gravis (28, 29), insulin-dependent diabetes mellitus (30), and the Evans’ syndrome (31), a disorder characterized by autoimmune hemolytic anemia, AITP, and the presence of a positive direct antiglobulin test. In addition, the Evans’ syndrome may also be associated with Hashimoto’s thyroiditis (32). Genetic predisposition to both Graves’ disease and AITP is highlighted by the familial occurrence of these two disorders in three female relatives, all of whom were positive for HLA-B8 and DR3 haplotypes (23). In addition, several other etiologic mechanisms have been proposed to link Graves’ disease and AITP. Underlying abnormalities in B and T cell functions with monoclonal or oligoclonal expansion of B cells may lead to the production of antibodies against thyroid and platelet antigens (17). Recently, this concept has gained support by the observation that TSH-R antibodies bind to truncated actin binding protein (TABP), a thyroid-derived protein (33). Intriguingly, TABP structurally links platelet glycoprotein GP Ibα and the high-affinity Fc receptor for IgG to the cytoskeleton of platelets. Thus, it is possible that, in patients with Graves’ disease, platelet destruction may result from recognition of platelet epitopes by TSH-R antibodies. A case series of three patients (34) and our personal experience in an unpublished series of seven patients (L.C Hofbauer, S Schmauss, A E Heufelder, unpublished observation) suggest that control of hyperthyroidism and restoration of a euthyroid state by antithyroid drug therapy may alleviate thrombocytopenia in some patients with Graves’ disease. Direct or indirect immunomodulatory effects of antithyroid drugs on both the underlying hyperthyroid state and the associated autoimmune disorder may contribute to the beneficial effects of antithyroid drug therapy on either disorder (35).

In a longitudinal study on 214 patients with Graves’ hyperthyroidism, 43% revealed thrombocytopenia (platelet <150 000/µl) prior to initiation of antithyroid drugs (8). Following initiation of antithyroid drug therapy, 28% of patients continued to reveal thrombocytopenia while still being hyperthyroid, whereas thrombocytopenia persisted in only 6% of patients following reinstitution of a euthyroid state (8). However, another clinical case report suggested that, in AITP and Graves’ disease, no relationship exists between thyroid...
function and platelet counts (36). For practical purposes, physicians should be aware of thrombocytopenia as a potential complication of Graves’ disease, and thyroid function should be evaluated in all patients with unexplained thrombocytopenia. Other disorders associated with AITP include autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis, malignancies (lymphoma, solid tumors) and certain viral infections, including human immunodeficiency virus infection (37).

In addition, AITP has also been reported in patients with Hashimoto’s thyroiditis (16, 38), and both diseases may further be associated with myasthenia gravis (39, 40). Moreover, an association between Graves’ disease and congenital prekallikrein (Fletcher factor) deficiency, a coagulation disorder characterized by marked prolongation of partial thromboplastin time, has been reported (41, 42). Finally, a patient in whom autoimmune factor VIII deficiency and Graves’ disease developed simultaneously has recently been described (43).

**Graves’ disease and the antiphospholipid syndrome**

Antiphospholipid syndrome represents a hypercoagulable state that is characterized by recurrent venous and arterial thromboses and the presence of antibodies directed against a heterogenous group of phospholipids, including cardiolipin and the lupus coagulant (44). Compared with healthy individuals, patients with Graves’ disease display an increased incidence of elevated antiphospholipid antibody titers (4, 45). In addition to the presence of elevated antiphospholipid antibody titers, these patients also revealed an increased thrombin activity (170% as compared with controls), both of which may contribute to the hypercoagulable state in Graves’ disease (4). The resulting hypercoagulable state may account, at least in part, for the higher incidence of thromboembolic events in patients with thyrotoxic Graves’ disease and atrial fibrillation as compared with euthyroid patients with atrial fibrillation due to nonvalvular etiologies (13). Conversely, patients suffering from the primary antiphospholipid syndrome, i.e. patients with an antiphospholipid syndrome in the absence of systemic lupus erythematosus, reveal an increased prevalence of thyroid autoantibodies (13). Although elevated antibody titers most likely reflect epiphenomena of the underlying autoimmune disorders, there are two recent case reports suggesting a closer link between Graves’ disease and antiphospholipid syndrome. In the first case, a 33-year-old woman with active Graves’ disease suffered a major ischemic cerebral infarction and was subsequently found to have markedly elevated titers of antiphospholipid antibodies (46). In the absence of antiphospholipid antibodies and the lupus anticoagulant, these data established the diagnosis of an incomplete form of antiphospholipid syndrome. In the second patient, a 48-year-old woman, multiple recurrent venous thromboses due to primary antiphospholipid syndrome occurred in close temporal relationship with severe Graves’ hyperthyroidism and ophthalmopathy (47). In the latter patient, presence of HLA DR7 antigen, excessively elevated titers of antiphospholipid antibodies and markedly elevated titers of autoantibodies directed against the TSH-R were documented. There are several possibilities as to how Graves’ disease and the antiphospholipid syndrome may be causally linked. Based on immunogenetic analyses of family members with autoimmune disorders and increased antiphospholipid antibody levels, presence of HLA DR4 and DR7 antigens may predispose patients with Graves’ disease and elevated levels of antiphospholipid antibodies to develop the full clinical picture of antiphospholipid syndrome with recurrent venous and arterial thromboses (48). Although mere coincidence remains a possibility, several hypotheses of a pathogenetic link can be envisioned: since antiphospholipid antibodies are thought to act through altering the structure of β₂-glycoprotein I, a lipid-binding inhibitor of coagulation (49, 50), one might speculate whether cross-reactivity between β₂-glycoprotein I and epitopes of the TSH-R might be responsible for the close temporal relationship of Graves’ disease and antiphospholipid syndrome. Another possibility is suggested by the recent clinical observation of a patient with benign monoclonal gammopathy, who presented with severe Graves’ hyperthyroidism, ophthalmopathy, and pretibial dermopathy (51). Thus, immunoglobulins directed against shared antigenic determinants may interact with both β₂-glycoprotein I and the TSH-R. Alternatively, TSH-R stimulating antibodies may be generated to act as anti-idiotypic antibodies against antiphospholipid antibodies.

**Antithyroid drugs and coagulation disorders**

In contrast to agranulocytosis, drug-induced thrombocytopenia during treatment with antithyroid drugs (carbimazole, methimazole, propylthiouracil) is very rare (52). In a retrospective analysis of 1256 consecutive patients with hyperthyroidism, 53% of whom had Graves’ disease, thrombocytopenia (defined as peripheral platelet count below 100 000/µl) occurred in only 0.2% of patients receiving antithyroid drugs and was not associated with clinically significant hemorrhage (53). However, variability of platelet counts during the course of Graves’ disease, due to the intrinsic dynamic of the disease and the beneficial effects of antithyroid drugs, makes it difficult to attribute to antithyroid drugs any specific role in the pathogenesis of thrombocytopenia.

Thrombocytopenia as a part of aplastic anemia due to treatment with antithyroid drugs is estimated to occur in 0.002 to 0.05% of patients, and manifests independently of time, cumulative exposure and type of
antithyroid drug employed (54). Onset of aplastic anemia, although unpredictable, usually occurs within the first 3 months following initial drug exposure. Compared with other forms of aplastic anemia, patients with thionamide-induced bone marrow failure tend to recover quickly, usually within 1 to 4 weeks (54). This may account for the relatively good prognosis with only one death in 11 fully documented cases, even when granulocyte-macrophage colony-stimulating factor is not administered.

Coagulation disorders in hypothyroidism

Although frank coagulopathy represents an unusual manifestation of thyroid hormone deficiency, patients with hypothyroidism exhibit minor bleeding tendency, which may manifest as menorrhagia or easy bruising (55). Menorrhagia may result from breakthrough bleeding secondary to anovulation, a common sequela of hypothyroidism. Easy bruising may be facilitated by myxedematous transformation of the perivascular extracellular matrix (56). In rare instances, severe hemorrhage may develop in patients with myxedema following trauma or surgery, if the hypothyroid state goes unrecognized and, thus, is not corrected (Table 2).

Platelet abnormalities in hypothyroidism

Counts and mean volume of platelets are usually normal or mildly decreased in hypothyroid patients (9). These abnormalities are not associated with coagulation abnormalities, and generally reverse to normal following institution of thyroid hormone replacement. However, bone marrow megakaryopoiesis may be reduced, even in the presence of normal peripheral platelet counts (56). In rare instances, patients with severe hypothyroidism and extensive accumulation of extracellular matrix in the bone marrow (‘marrow myxedema’) may reveal severe, inhibition of megakaryopoiesis (57). In contrast, patients with hypothyroidism due to Hashimoto’s thyroiditis andAITP may display low platelet counts as a result of peripheral consumption of platelets, whereas megakaryopoiesis by an adequately responding bone marrow is increased (16).

Abnormalities of platelet metabolism reported to occur in hypothyroidism include decreased activity of platelet membrane phospholipid-derived platelet factor 3 (58) and reduced release of serotonin from platelets following aspirin challenge (59). Consequently, drugs such as α-methyldopa and aspirin may unmask or aggravate platelet dysfunction, and thus should be cautiously administered to hypothyroid patients (56, 59, 60).

Acquired von Willebrand’s disease

Abnormalities of primary hemostasis in hypothyroidism resemble acquired von Willebrand’s disease, and may present with episodes of mucomucutaneous bleeding (nose or gingival bleeding, menorrhagia and gastrointestinal bleeding), increased sensitivity to aspirin challenge, and major hemorrhage following trauma or surgery (2, 61, 62). Mechanisms involved in hypothyroidism-associated acquired von Willebrand’s disease include decreased activity of factor VIII/von Willebrand factor complex, impaired ristocetin cofactor activity and reduced platelet adhesiveness. Collectively, these mechanisms may lead to an elevated partial thromboplastin time, decreased platelet aggregation and prolonged bleeding time (2, 56). Factor VIII assessment indicated that decreased levels of factor VIII antigen contribute significantly to the increased bleeding tendency in hypothyroid subjects, whereas factor VIII activity remains normal (63).

Acquired von Willebrand’s disease in hypothyroid subjects may be difficult to diagnose by routine laboratory studies unless specifically suspected. In addition, the insidious onset of hypothyroidism and the subtle clinical signs and symptoms of chronic autoimmune thyroiditis may make detection of an associated coagulopathy an even more difficult task. Thus, correct diagnosis is frequently not established until bleeding tendency is unmasked by trauma or

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<tr>
<th>Table 2</th>
<th>Coagulation disorders associated with hypothyroidism.</th>
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<tbody>
<tr>
<td>Parameter</td>
<td>Selected references</td>
</tr>
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<td>Platelets</td>
<td>Reduced peripheral platelet counts (9)</td>
</tr>
<tr>
<td>Coagulation factors</td>
<td>Decreased mean platelet volume (9)</td>
</tr>
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<td></td>
<td>Reduced megakaryopoiesis (56)</td>
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<td></td>
<td>Marrow myxedema (57)</td>
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<td></td>
<td>Decreased activity of factors VII, VIII, IX, X (56)</td>
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<td></td>
<td>Increased biological half-life of factors II, VII, IX, X (56)</td>
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<td></td>
<td>Requirement of higher Warfarin doses (16, 38)</td>
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<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>(61–63)</td>
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<tr>
<td>Acquired von Willebrand’s disease</td>
<td>(58, 59)</td>
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surgery, or until patients undergo a thorough evaluation of their coagulation status (61–63). Therefore, thyroid function tests should be obtained in all patients with otherwise unexplained bleeding tendencies or coagulopathies.

It has recently been suggested that acquired von Willebrand’s disease may represent a general feature of hypothyroidism that is completely reversed by replacement with thyroid hormone (2, 61, 62). Several hypotheses have been put forward to explain how reversal of von Willebrand’s disease may be linked to institution of thyroid hormone therapy in hypothyroid individuals (61). Von Willebrand factor may be released from endothelial cells, reflecting their increased sensitivity to epinephrine following administration of thyroid hormone. Similar mechanisms have been reported for angiotensin-converting enzyme (64, 65), thrombomodulin (66) and endothelin-1 (67). In addition, increased de novo synthesis of von Willebrand factor and factor VIII in hypothyroid patients following thyroid hormone replacement may also result from non-specific stimulation of hepatic protein synthesis by thyroid hormone (55).

In view of the potential role of hypothyroidism in promoting enhanced bleeding, every patient with unexplained hemorrhage should have his thyroid function evaluated. This approach permits rapid identification of patients with hypothyroidism, an easily treatable subgroup. In addition, patients with myxedema coma should have their coagulation parameters closely monitored both prior to and during administration of thyroid hormones.

**Coagulation factors and fibrinolytic activity in hypothyroidism**

Various abnormalities of coagulation factors and fibrinolytic markers have been reported to occur in hypothyroidism (for review see (56)). Decreased hepatic protein synthesis in hypothyroidism together with varying rates of synthesis of coagulation factors may explain why some factors (fibrinogen, V) are normal, while others (VII, VIII coagulant activity, ristocetin cofactor, IX, XI, XII) are decreased (1, 56, 68). In addition, there is evidence that the biological half-life of coagulation factors II, VII, IX and X may be increased in hypothyroid patients (56). Impaired clearance of these factors may explain the clinical observation that higher doses of warfarin may be required to achieve appropriate anticoagulation in hypothyroidism (56). Coagulation studies in hypothyroidism typically reveal normal thrombin time, increased partial thromboplastin time, and normal or slightly decreased prothrombin time, all of which normalize readily following replacement with thyroid hormone (2, 56). Furthermore, hypothyroid individuals display an increased fibrinolytic activity with increased plasminogen and plasmin activity that is reversed by administration of thyroid hormones (69). Abnormalities of fibrinolysis resulting from thyroid hormone deficiency may be explained, in part, by decreased hepatic protein synthesis.

**Coagulation disorders associated with thyroid carcinoma**

Clinical observations of coagulation disturbances in patients with thyroid carcinoma are limited. There is one recent case report describing a patient with medullary thyroid carcinoma and elevated levels of carcinoembryonic antigen and calcitonin who was found to have marked paraneoplastic hypercoagulability with increased blood viscosity in the presence of normal coagulation studies (70). This patient’s hypercoagulable state became apparent only after manifestation of deep venous thrombosis and thrombosis of the superior sagittal sinus. Interestingly, following surgical debulking of the tumor and involved lymph nodes, blood viscosity normalized and no recurrence of thrombosis was observed. In addition, development of spontaneous consumption coagulopathy leading to lethal hemorrhage has been reported in a dog with anaplastic thyroid carcinoma (71). To our knowledge, no such association has yet been reported in humans.

**Conclusions**

Disturbances of coagulation represent a common phenomenon in patients with thyroid diseases. In recent years, clinical, immunological and immunogenetic studies have provided significant progress in the understanding of their pathogenesis. Physicians should be aware of the spectrum of coagulation disturbances that may occur in patients with thyroid diseases, ranging from laboratory abnormalities and subclinical disturbances to severe or lethal hemorrhage or thromboembolism. Given the associations of Graves’ disease andAITP, and that of hypothyroidism and acquired von Willebrand’s disease, thyroid function tests should be performed early in the assessment of patients with these disorders. Furthermore, patients with an established diagnosis of hyperthyroidism and atrial fibrillation should receive appropriate anticoagulation, especially when combined with additional risk factors. Further progress in our understanding of the underlying mechanisms of coagulation disorders in thyroid diseases is likely to reveal important insights into their pathology and more sophisticated therapeutic strategies.

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