Review Article

The haematology of hyperthyroidism: abnormalities of erythrocytes, leucocytes, thrombocytes and haemostasis

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Summary: The abnormalities of erythrocytes, leucocytes, thrombocytes and coagulation that have been reported, particularly in more recent years, to be associated with hyperthyroidism are surveyed. Several areas are highlighted where further investigations could lead to clinically useful insights, improved information about the haematological processes involved or to a better understanding of thyroid hormone action.

Introduction

Although clinically important haematological abnormalities are unusual in patients with hyperthyroidism, the haematological system is, nonetheless, greatly affected by the thyrotoxic state. Hyperthyroidism can have different causes, the more common of which are autoimmunity (Graves' disease), toxic adenomas (multinodular goitre or single nodule), or the administration of thyroid hormone (used to induce experimental hyperthyroidism). Graves' disease is responsible for most cases of clinical hyperthyroidism, particularly in younger patients. Some of the haematological abnormalities that occur may depend on the cause of the hyperthyroidism. For example, in Graves' disease certain haematological changes may have an immunological basis rather than being caused by thyroid hormone excess per se.

Because understanding of the mechanisms of action of thyroid hormones is incomplete, most of the haematological changes that have been reported cannot be adequately explained. Recent advances in our understanding of thyroid hormone action at the cellular level have been recently reviewed. In hormone-responsive tissues, nuclear receptors for tri-iodothyronine (T₃) are present and are involved in the initiation of hormone action. The receptors have been identified as non-histone proteins of molecular weight about 50,000. Recent work has suggested that the receptor is closely related to the product of the cellular proto-oncogene c-erb-A and thus is a member of the family of receptors that includes those for steroid hormones, vitamin D and retinoic acid. After binding to the receptor, it is postulated that the T₃-receptor complex binds to specific regions of the DNA and alters gene expression. Whether or not thyroid hormones can initiate cellular responses through direct interaction with extranuclear components, such as mitochondria or receptors on the plasma membrane, remains an open question. It is likely that careful study of certain of the haematological abnormalities in hyperthyroidism would lead to major advancements in our understanding of the mechanisms of action of thyroid hormones. The stimulatory effect of thyroid hormones on glucose metabolism in the erythrocyte, a cell without mitochondria or a nucleus, is an example. On a more clinical level, there is a need for a simple, reliable assay of the effects of thyroid hormones at the tissue level. The measurement of the basal metabolic rate has proved unwieldy, unreliable and imprecise in many instances. Currently, the physician relies largely on indirect measures such as hormone levels in blood and clinical evaluation to ascertain the thyroid hormone status of patients. Although these measures are often sufficient, haematological abnormalities offer the potential of making a major contribution in this area.

This review attempts to survey many of the abnormalities of erythrocytes, leucocytes, thrombocytes and coagulation that have been reported,
particularly in more recent years, to be associated with hyperthyroidism and to highlight the areas where further investigations are needed to increase our understanding of the mechanisms involved. In most instances, we have not compared the haematological change seen in hyperthyroidism with the change, or lack thereof, that has been reported in hypothyroidism. To do so regularly would have extended the review unduly. The well-known association of pernicious anaemia with Graves' disease has been extensively reviewed2,3 and will not be further discussed in this review.

Erythrocytes

Kinetics and indices (Table I)

The earlier studies on erythrocyte kinetics in hyperthyroidism have been comprehensively reviewed.5-3 The total red blood cell mass is increased4-6 even though the survival time of erythrocytes is shortened, at least in some patients.5-7,8 Total red cell mass is directly related to lean body mass and the suggested basis for this correlation is that oxygen-carrying power (the red cell mass) is regulated by the basal oxygen requirements of the actively-metabolizing lean body mass;4 the oxygen requirement of adipose tissue being relatively low. Total blood volume is also related to the oxygen requirement as expressed by the basal metabolic rate, and is elevated in hyperthyroidism.9 The observation that indices such as haematocrit, haemoglobin and red cell count are not elevated in hyperthyroidism despite an increase in total red cell mass has been attributed to this concomitant increase in plasma volume.5-9 Frank polycythaemia, however, may be seen on rare occasions.6

The mechanism whereby thyroid hormones increase erythropoiesis is not entirely clear. There is evidence that erythropoietin levels are increased, probably in response to increased cellular oxygen need.4,5,10 In vitro culture studies suggest that thyroid hormones directly stimulate erythroid progenitor cells and that this effect may be mediated via \( \beta_2 \)-adrenergic receptors.11-12 Recently evidence has been presented suggesting that the stimulating effects of thyroid hormones on erythropoiesis is not direct, but is mediated via mononuclear cells which release tissue-specific erythropoietin-stimulating factor(s) on exposure to thyroid hormones.13

The increase in erythropoiesis in hyperthyroidism is reflected in the bone marrow which undergoes erythroid hyperplasia.5,14-15 Ferrokinetic data confirm that haemoglobin synthesis is increased; in the thyrotoxic patient the plasma iron clearance time is shortened and the plasma iron turnover and red blood cell radioiron incorporation increased.5,16-17 In some patients, however, there is evidence of ineffective erythropoiesis. Lahtinen18 examined the bone marrow of 19 thyrotoxic patients both before therapy and after euthyroidism had been attained. The proportion of sideroblasts and the amount of haemosiderin were significantly higher when the patients were hyperthyroid and the marrow contained pathological sideroblasts with coarse, perinuclear iron granules. Further evidence that ineffective erythropoiesis may occur is that some thyrotoxic patients show reduced iron utilization17 and a reduced mean corpuscular volume is frequently observed.18-21 It has been suggested that these manifestations of ineffective erythropoiesis are most likely to be found in those patients with very severe or long-standing thyrotoxicosis.17

The reduced mean corpuscular volume observed in hyperthyroidism contrasts with the macrocytosis of hypothyroidism and points to a role for thyroid hormone in determining erythrocyte size.

As a result of the above described variations in erythropoiesis and the changes in plasma volume which occur in the hyperthyroid patient, it is not surprising that the haemoglobin level may be high, low or normal. In the majority of patients, however, the routine full blood count is essentially normal with minimal changes in the haemoglobin level, red cell count, mean corpuscular volume, reticulocyte count14 or blood viscosity.22 If, as is often the case, there is also a deficiency of iron, vitamin B\(_{12}\) or folate, the characteristic features of these deficiencies will be seen. Iron deficiency, in particular, is commonly seen since the majority of hyperthyroid patients are menstruating females. Since hyperthyroidism may interfere with the ability of the marrow to utilise iron, a poor response to iron therapy may be seen.17

Biochemistry (Table II)

Most,23-29 but not all,30 investigators have found the activity of the Na\(^+\), K\(^+\)-ATPase in human erythrocyte membranes to be decreased in hyperthyroidism and to be associated with an increase in intracellular sodium concentration.27,29-33 The number of moles of ouabain that bind per red cell

Table I Abnormalities of erythrocyte kinetics and indices in hyperthyroidism

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Increase/Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mass</td>
<td>Increased4-6</td>
</tr>
<tr>
<td>Erythropoiesis</td>
<td>Increased5</td>
</tr>
<tr>
<td>Iron turnover</td>
<td>Increased5,6,17</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin</td>
<td>Decreased18-21</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Decreased18-21</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Decreased18-20</td>
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<tr>
<td>Haematocrit</td>
<td>Decreased18-20</td>
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is decreased\textsuperscript{26-29} which suggests that a decrease in the number of Na\textsuperscript{+}, K\textsuperscript{+}-ATPase sodium pumps per cell is responsible for the decrease in sodium efflux rather than a defect in performance of the pumps. A significant inverse relationship has been observed between the number of sodium pumps per erythrocyte and the plasma thyroxine and tri-iodothyronine levels.\textsuperscript{27-34} It has been suggested\textsuperscript{25-28} that the effects of thyroid hormone on the activity of the Na\textsuperscript{+}, K\textsuperscript{+}-ATPase are not specific but are a manifestation of a widespread effect on the metabolism or membrane environment of most surface proteins of the erythrocyte. However, extensive studies of the function and environment of erythrocyte surface proteins in hyperthyroidism have not been carried out and some of the existing data are controversial. For example, one group\textsuperscript{28} has reported a significant reduction in the number of insulin receptors per red blood cell in hyperthyroidism together with a significant increase in their average affinity, whereas another group\textsuperscript{35} has reported a marked decline in insulin binding affinity without change in insulin receptor number. The proposal\textsuperscript{36-37} that a generalized increase in Na\textsuperscript{+}, K\textsuperscript{+}-ATPase activity is responsible for a major proportion of the increased energy demand in hyperthyroidism appears not to include the erythrocyte.\textsuperscript{33} It may be\textsuperscript{26} that the erythrocyte, being unable to carry out protein synthesis, cannot adequately replace certain proteins, such as components of the Na\textsuperscript{+}, K\textsuperscript{+}-ATPase sodium pump, whose rate of catabolism is increased in hyperthyroidism.\textsuperscript{38} On the other hand, Ca\textsuperscript{2+}-ATPase activity of erythrocyte membranes was found to be increased in hyperthyroidism\textsuperscript{39} which suggests that no single explanation for the effect of thyroid hormone on components of the plasma membrane of the erythrocyte is likely.

There is general agreement that erythrocyte zinc concentration is reduced in hyperthyroidism\textsuperscript{27,32,40-42} and that urinary zinc excretion is increased.\textsuperscript{41-42} The concentration of the B isoenzyme of carbonic anhydrase, which is by far the most abundant zinc metalloenzyme in the erythrocyte, is decreased in hyperthyroidism, whereas the concentration of the genetically distinct C isoenzyme is near normal.\textsuperscript{43-46} For example, Funakoshi and Deutsch\textsuperscript{46} found the mean levels of the B and C isoenzymes to be 37% and 80% of normal, respectively. The overall activity of carbonic anhydrase is decreased, but the activities of a number of other zinc metalloenzymes of the erythrocyte are unchanged in hyperthyroidism.\textsuperscript{40} It is likely that thyroid hormones specifically inhibit the synthesis of the B isoenzyme. This effect has not been associated with a change in erythrocyte function nor is it of sufficient magnitude to explain the negative zinc balance that occurs in thyrotoxicosis,\textsuperscript{41,42} a phenomenon which has been correlated with the overall catabolic state.\textsuperscript{41}

Erythrocytes, which lack mitochondria, metabolise glucose via the Embden-Meyerhoﬀ glycolytic pathway and the hexose monophosphate shunt (also called the pentose phosphate shunt). ATP, the major energy source, is produced by the Embden-Meyerhoﬀ pathway and the hexose monophosphate shunt yields NADPH which is used as a cofactor in a number of reactions. Oxygen consumption and heat production by erythrocytes from hyperthyroid patients are both increased\textsuperscript{47,48} and increased activities of a number of enzymes of intermediary metabolism in erythrocytes from hyperthyroid patients have been reported.\textsuperscript{32-49} Normally, most of the available glucose is utilized by the Embden-Meyerhoﬀ pathway\textsuperscript{50} and recently it was reported\textsuperscript{51} that the metabolic activities of both pathways are proportionately increased in hyperthyroidism so that the Embden-Meyerhoﬀ pathway continues to predominate. The mechanism by which thyroid hormones increase the metabolic activity of the erythrocyte is unknown but is of special interest since the erythrocyte lacks the two organelles which are usually postulated to be involved in the mechanism of action of thyroid hormones in other tissues, namely mitochondria and a nucleus.

In erythrocytes from hyperthyroid patients and from normal subjects treated with thyroid hormone the haemoglobin dissociation curve is shifted to the right indicating a decreased affinity for oxygen.\textsuperscript{52-53} A result of this shift is that oxygen is more readily delivered to peripheral tissues, perhaps to meet the increased metabolic demands of thyrotoxicosis. It is known\textsuperscript{54-55} that an increase in the concentration of organic phosphates within erythrocytes displaces the oxyhaemoglobin dissociation curve to the right. It has been reported that the concentration of 2,3-diphosphoglycerate, the major source of organic phosphate in the erythrocyte, is increased after
incubation in vitro of red cell preparations from normal subjects in medium containing thyroid hormones and in the erythrocytes of some, but not all, patients with hyperthyroidism.

The activities of erythrocyte catalase and monoester lipase are increased in hyperthyroid patients but the mechanism and possible significance of these changes are unclear. The mean percent haemoglobin A₂ level (3.21) in a group of untreated hyperthyroid subjects was significantly (P < 0.001) higher than in a group made euthyroid with antithyroid drugs (2.42). These results, which confirmed an earlier report, suggest that thyroid hormones can modulate the synthesis of globin chains. A slight elevation of the foetal haemoglobin percentage has also been reported.

Leucocytes

Absolute and relative numbers

An association between neutropenia and Graves' disease has been recognized for at least 80 years. In relatively recent studies, the incidence of absolute neutropenia in hyperthyroid patients varied from less than 5% to 18%. A significant relative neutropenia in thyrotoxic patients, originally described in 1908, has also been confirmed in more recent years. Treatment of the neutropenic thyrotoxic patient with radioiodine or propylthiouracil usually results in a return of the neutrophil count to normal and neutropenia detected before treatment does not contraindicate the use of thioamide drugs. The aetiology of the neutropenia is unknown, but does not appear to involve depressed or ineffective myelopoiesis.

Although there is general agreement that a relative lymphocytosis is often seen in hyperthyroid patients, there is less consensus regarding whether an absolute lymphocytosis is or is not associated. There has also been disagreement regarding the relative and absolute numbers of T lymphocytes and subsets. Table III gives the findings of several recent reports. The conflicting results are further complicated by the fact that the mean changes reported in a study often do not occur in all patients in that study. For example, one group found a decrease in the proportion of suppressor T lymphocytes in only about 50% of patients. The lack of consistent findings in peripheral blood may be due to the fact that the pathogenetic immunological events in Graves' disease take place within the thyroid gland. Atypical lymphocytes may be seen in some patients with thyrotoxicosis.

There have been surprisingly few investigations of possible changes in the metabolism of leucocytes in hyperthyroidism. In one study it was found that leucocyte Na⁺, K⁺-ATPase activity, [³H]ouabain binding capacity (an indicator of the number of sodium pumps) and total active rubidium influx (used to measure potassium flux) were all significantly increased in untreated hyperthyroidism. There was no change in leucocyte sodium concentration. These results contrasted with those found in erythrocytes which showed decreased Na⁺, K⁺-ATPase activity, decreased [³H]ouabain binding capacity and decreased active potassium flux rates.

Biochemistry

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A statistically significant decrease in phagocytic ability and an increase in nitroblue tetrazolium reduction by neutrophils from hyperthyroid patients compared to normal control subjects has been reported. Cytochemical observations suggested increased activity of leucocyte acid phosphatase and β-glucuronidase. Further studies of granulocyte function and metabolism in hyperthyroidism are needed.

Insulin binding to monocytes was found to be significantly decreased in a group of hyperthyroid patients as compared to a control group. The decrease was attributed to a decrease in receptor number rather than receptor affinity. It was suggested that peripheral insulin resistance might contribute to the glucose intolerance of thyrotoxicosis.

Several groups have studied the effects of thyrotoxicosis on the adrenergic receptor system of mononuclear leucocytes. It is generally agreed that there is an increase in the number of β-adrenergic receptors per cell. If, as some believe, hyperthyroidism is associated with an increased sensitivity to circulating catecholamines, it is possible that the mechanism involves a thyroid hormone-induced increase in adrenergic receptor density in a variety of responsive tissues.
Platelets and other coagulation factors

Mean platelet volume was found to be increased in hyperthyroidism and the mean platelet distribution width, which represents the coefficient of variation of the mean platelet width, was decreased. The lower mean value of the platelet distribution width observed in hyperthyroid patients suggested that platelet size was more uniform than in the euthyroid state. A larger, more uniform population of platelets in hyperthyroidism is consistent with the view that platelet lifespan is decreased but does not indicate the mechanism(s) involved. In fact, a shortened platelet survival time and an increase in megakaryocytes in bone marrow have been reported in hyperthyroid subjects even when platelet counts were normal.

There is a paucity of recent studies of platelet function and biochemistry in hyperthyroidism. Platelet adhesiveness, measured in vitro using glass beads, was found to be significantly increased in thyrotoxicosis and a decrease to normal was noted after treatment-induced euthyroidism. Platelet monoamine oxidase activity has been reported to be normal and decreased in hyperthyroid subjects. Earlier studies also gave conflicting results perhaps due to different assay techniques used, different animal species studied and the wide variety of tissues investigated in addition to platelets. In another study, 8 of 22 patients with Graves' disease and normal platelet counts were found to have elevated platelet-bound IgG and in these cases abnormal in vitro platelet aggregation measurements were observed, particularly with epinephrine.

The uncommon but well recognized association between hyperthyroidism and immune thrombocytopenia continues to be the subject of case reports. In a substantial number of cases, a marked improvement or permanent reversal of the thrombocytopenia occurred after correction of the hyperthyroidism and it is recommended, therefore, that glucocorticoid treatment of the immune thrombocytopenia should be continued until the patient has been euthyroid for about 4 weeks before considering additional immuno-suppressive therapy or splenectomy. The exact mechanism for the thrombocytopenia has not been established; however, platelets from such patients show elevated levels of bound immunoglobulins. It has been pointed out that platelet-bound IgG may not be specific for any platelet antigen, but rather may exist as part of an antigen-antibody complex bound to the Fc receptor of the cell.

Aside from possible functional abnormalities of platelets, the causes for the easy bruising and menorrhagia that are associated with hyperthyroidism have not been established. In fact, the mean levels of fibrinolytic activity and of plasminogen were reported to be significantly reduced in hyperthyroid patients and the mean levels of coagulation factor VIII and related properties significantly increased. Probably related to this effect on factor VIII is the significantly shortened partial thromboplastin time in hyperthyroid patients. Simone et al. observed no change from normal in clotting factors II, V, IX and X in hyperthyroid subjects; a significant depression of factor II levels has subsequently been reported by others, however. When hyperthyroid patients receive warfarin, the decreases in factors II and VII are significantly greater than the effects observed in euthyroid subjects. This result in the hyperthyroid patient being more sensitive to the anticoagulant effects of warfarin. It is not clear how thyrotoxicosis causes these changes in coagulation function, but the altered response necessitates careful monitoring in such patients.

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H. C. Ford and J. M. Carter

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