

Review Article

Haemostasis in hypothyroidism

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Summary: Abnormalities that have been reported for platelet indices and function, coagulation factors and tests, and the fibrinolytic system in hypothyroidism are reviewed. These abnormalities, although usually of limited importance clinically, may occasionally lead to major bleeding episodes and to diagnostic confusion.

Introduction

A bleeding tendency, usually manifested by easy bruising and menorrhagia and occasionally by severe bleeding episodes, has been recognized in hypothyroid patients, and a number of abnormalities of platelets and of the circulating clotting and fibrinolytic systems have been described. The pathogenesis of the bleeding tendency associated with thyroid hormone deficiency is usually multifactorial and the contribution of defects in platelets and clotting factors may be relatively minor. For example, the menorrhagia, which is a frequent complaint, is probably primarily due to oestrogen breakthrough bleeding secondary to the anovulation that accompanies thyroid hormone deficiency.^{1–3} Also, myxoedematous changes in the extracellular matrix surrounding the superficial blood vessels rather than changes in the circulatory haemostatic mechanisms may play a leading role in promoting easy bruising.

Platelets (Table I)

Platelet counts have usually been reported to be normal in hypothyroid patients and no significant changes have been noted following thyroid hormone administration.^{4–10} There have, however, been several contrary reports. In man¹¹ and rat¹² a significant fall in platelet count was observed after induction of hypothyroidism. On the other hand, it was reported¹³ that the platelet count increased significantly within two weeks after discontinuing triiodothyronine in a group of patients previously rendered athyreotic because of thyroid carcinoma. These latter authors¹³ also reported that the mean platelet volume decreased and the platelet distribu-

Table I Platelet indices and function in hypothyroidism

Platelet count	– unaffected ^{4–10} – decreased ^{11,12} – increased ¹³
Mean platelet volume	– unaffected ¹⁰ – decreased ¹³
Platelet distribution width	– unaffected ¹⁰ – increased ¹³
Decreased adhesiveness	^{5,6}
Decreased aggregability	^{5,16,17}
Decreased platelet factor	^{3,7}
Decreased heat production	²⁷
Abnormal response to aspirin	¹⁸
Abnormal prostaglandin metabolism	¹²
Monoamine oxidase activity	unchanged ^{4,9}
Increased bleeding time	^{5,6,22,23}

tion width increased after discontinuation of triiodothyronine. It is possible that the doses of triiodothyronine were sufficient to render the patients mildly hyperthyroid and this was responsible for the smaller platelet distribution width and greater mean platelet volume observed in the patients when receiving treatment. We have shown¹⁴ that hyperthyroidism is associated with an increase in mean platelet volume and a decrease in platelet distribution width. The increased platelet count reported by van Doormaal *et al.*¹³ in hypothyroid patients is unexplained and contrary to the findings of others. It may represent an acute change, not seen in the usual chronically hypothyroid patient. The bone marrow of hypothyroid patients may show a diminution in megakaryocytes even when the peripheral platelet counts are normal.⁴ Occasionally, the bone marrow may undergo gelatinous transformation.¹⁵

Two studies^{5,6} have shown that platelets from the majority of the hypothyroid subjects studied were less adhesive to glass beads than normal and that

this defect was corrected by the administration of thyroid hormones. Platelets from hypothyroid patients have also been observed to aggregate only weakly in the presence of ADP, adrenaline and a connective tissue extract.¹⁶ Normal aggregation responses were observed after one week's treatment of the patients with triiodothyronine. Depression of platelet aggregability has also been noted in hypothyroid rats.¹⁷ Others⁵ reported normal aggregation responses to standard concentrations of aggregating agents by platelets from hypothyroid patients; however, the lowest concentration of adrenaline that just began to produce primary aggregation was much higher with platelets from hypothyroid patients than with those from normal subjects.

Platelet factor 3 activity, which may originate from phospholipids of the platelet plasma membrane, was found to be reduced in hypothyroid patients.⁷ The total concentration of phospholipids in hypothyroid platelets was lower than normal, but there was no discernible correlation between changes in factor 3 activity and phospholipid concentration.

Thrombin-induced platelet serotonin release following aspirin ingestion was found to be subnormal in hypothyroid patients.¹⁸ However, only patients with markedly elevated thyroid stimulating hormone levels displayed an increased haemostatic sensitivity to aspirin as measured by bleeding time prolongation. It has also been suggested¹⁹ that methyl dopa can exaggerate the defective platelet function of hypothyroidism.

Although capillary fragility is said to be increased in hypothyroidism,²⁰ this appears to be largely a clinical observation without strong investigative evidence. Thomson²¹ studied 25 hypothyroid patients using a negative pressure test for estimating capillary fragility. Contrary to expectation, capillary fragility was found to be decreased in patients with spontaneous hypothyroidism (11 subjects) and not different from normal in 14 patients with iatrogenic hypothyroidism. The explanation for these results is unknown; the study needs to be repeated and extended. A number of studies have reported an increased bleeding time in hypothyroid patients.^{5,6,22,23}

Hashimoto's thyroiditis, a common cause of hypothyroidism, and Graves' disease are both autoimmune disorders of the thyroid and may be seen in association with other 'autoimmune' disorders such as pernicious anaemia, diabetes mellitus and adrenal insufficiency. It is surprising, therefore, that although an association is recognized between Graves' disease and autoimmune thrombocytopenic purpura,²⁴ no such association is recognized between Hashimoto's thyroiditis and autoimmune thrombocytopenia.²⁵ Circulating coagulation inhibitors, seen in autoimmune condi-

tions such as rheumatoid arthritis and systemic lupus erythematosus, are also rarely associated with hypothyroidism.²⁶

Heat production, determined by microcalorimetry, was significantly lower in platelets from hypothyroid patients and increased to normal during thyroxine treatment of the patients.²⁷ The authors point out that the decreased energy expenditure in platelets from hypothyroid patients might contribute to the abnormalities of platelet function that have been described. Also, it is not clear how thyroid hormones exert a calorimetric effect in platelets which lack nuclei.

The aetiology and pathogenesis of the abnormalities of platelet function that occur in hypothyroidism are unknown. There is evidence¹² that alterations in platelet and arterial wall prostaglandin production or metabolism occur in hypothyroidism and these may possibly contribute to the platelet dysfunction. Others have suggested²⁸ that abnormalities of platelet aggregation in autoimmune thyroid disease are caused by elevated levels of immunoglobulin G adherent to the platelets. The possible effects of decreased platelet energy metabolism on platelet function²⁷ have been referred to above.

Coagulation factors

The results of assays of coagulation factors and tests of coagulation in hypothyroid patients are given in Table II. The reported prevalence of abnormalities of these factors among hypothyroid patients differs widely. This variation undoubtedly reflects differences in the duration and severity of the hypothyroidism, differences in the methods of assay and reference ranges, and differences in the response to hypothyroidism among individual patients. In some patients the picture may resemble von Willebrand's disease;^{5,22,23,29} that is, decreased factor VIII coagulant and antigen activity (particularly a decrease in the von Willebrand factor antigen), impaired ristocetin cofactor activity, decreased platelet adhesiveness, a range of abnormal platelet aggregation tests, a normal platelet count and an increased bleeding time. Usually, these laboratory criteria are only partially fulfilled in hypothyroid patients. On the other hand, variability in the results of laboratory tests occur among different patients with naturally-occurring von Willebrand's disease and even at different times in the same patient.³⁰

It has been reported that the biological half-lives of factors II, VII, IX and X are increased in hypothyroid patients.³¹ After coumarin administration to hypothyroid patients a mean time of 41 hours was required for the prothrombin time to double as compared to a mean time of 24 hours in

Table II Coagulation factors and tests in hypothyroidism

Fibrinogen	– normal ^{22,42,44}
V	– normal ⁴⁴
VII	– decreased ⁵
VIII coagulant activity	– decreased ^{23,43,44,50} – normal ²²
ristocetin cofactor activity	– decreased ^{23,50}
related antigen	– decreased ^{22,50}
vWF antigen	– decreased ²³ – normal ²²
IX	– decreased ^{5,44}
XI	– decreased ^{5,44}
XII	– decreased ⁴¹
Thrombin time	– normal ^{5,22,23}
Partial thromboplastin time	– increased ^{5,7,22,23,41,44}
Prothrombin time	– normal ^{5,22,23,44} – decreased ³²

normal subjects. These findings have implications regarding the duration of heparin administration in hypothyroid patients receiving combined heparin-warfarin treatment. It has been suggested³² that more warfarin than usual may be required to achieve a satisfactory degree of anticoagulation in hypothyroid patients; however, there are few clinical reports to substantiate this suggestion.³³

The pathogenesis of the abnormalities of coagulation factors in hypothyroid patients is unknown. A direct, specific effect of thyroid hormone lack is considered unlikely in all instances, although this possibility has not been ruled out and it may apply to factor VIII deficiencies. Factor VIII levels are known to be increased in normal subjects by adrenaline administration^{34,35} and there is considerable evidence (reviewed in reference 36) that thyroid hormone alters the sensitivity of an individual to the metabolic effects of catecholamines. It was postulated that the deficiency of factor VIII that may occur in hypothyroidism was related to a relative insensitivity to endogenous adrenergic stimuli. However, a direct stimulatory effect of thyroid hormones on factor VIII synthesis or metabolism now seems more likely because it was shown³⁷ that an increase in factor VIII occurs in normal volunteers given thyroxine and the beta-adrenergic blocker, propranolol. This *in vivo* response to thyroxine administration differed from the lack of stimulation of the rate of accumulation of factor VIII-related antigen in the culture medium of cultured human umbilical cord endothelial cells in response to addition of thyroxine.³⁸ However, the *in vitro* lack of response to thyroxine that was observed does not necessarily indicate that thyroid hormone has no effect on factor VIII synthesis. It is generally agreed that thyroxine is an inactive prohormone in most tissues which is activated by deiodination to form

triiodothyronine. Certain tissues, such as hepatic, pituitary and central nervous system, have been shown to possess deiodinase activity, but not, to our knowledge, umbilical cord endothelial cells in culture. Some of the deficiencies in clotting factors that have been observed in hypothyroidism may be simply the result of the generalized decrease in protein synthesis that occurs.³⁹

Fibrinolytic activity of whole blood and plasma is increased in hypothyroidism and is diminished by the administration of thyroid hormone^{40,41} (Table III). The increased activity is accompanied by increase in plasminogen and, probably, by an increase in plasminogen activator.^{41,42,43} Fibrinogen levels remain normal.^{22,42,44} How thyroid hormones mediate these changes is unknown; the increase in sympathetic activity that accompanies hypothyroidism⁴⁵ may play a role as well as direct effects of thyroid hormone lack on specific or generalized protein synthesis. Modern techniques for investigating the fibrinolytic system need to be applied.

Discussion

Bleeding abnormalities are not usually important clinically in hypothyroid patients and it is reassuring to realise that two large series showed no excess blood loss or bleeding complications during or following surgery in hypothyroid patients.^{46,47} On the other hand, severe bleeding may occasionally accompany hypothyroidism⁴⁸ and may lead to diagnostic confusion.²² From a research point of view, study of the effects of thyroid hormone and its lack on certain components of the haemostatic system, for example effects on factor VIII synthesis or on platelet function and metabolism, may substantially advance understanding of the mechanism of action of thyroid hormone at the cellular level and may provide insight into the functioning and regulation of the haemostatic system itself.

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Table III Fibrinolytic system in hypothyroidism

Plasminogen	– increased ⁴²
Plasminogen activator	– normal ⁴² – increased ⁴¹
Inhibitor of plasma activation	– decreased ⁴²
Antiplasmin	– normal ⁴²
2-Macroglobulin	– increased ⁴¹
Antithrombin III	– decreased ⁴¹
Fibrinolytic activity	– increased ^{40,41}
Euglobulin lysis time	– increased ⁴³

References

- Goldsmith, R.E., Sturgis, S.H., Lerman, J. & Stanbury, J.B. The menstrual pattern in thyroid disease. *J Clin Endocrinol Metab* 1952, **12**: 846–855.
- Scott, J.C. & Mussey, E. Menstrual patterns in myxedema. *Am J Obstet Gynecol* 1964, **90**: 161–165.
- Longcope, C. The male and female reproductive systems. In: Ingbar, S.H. & Braverman, L.E. (eds) *The Thyroid*, 5th edition. J.B. Lippincott, Philadelphia, 1986, pp. 1194–1199.
- Axelrod, A.R. & Berman, L. The bone marrow in hyperthyroidism and hypothyroidism. *Blood* 1951, **6**: 436–453.
- Edson, J.R., Fecher, D.R. & Doe, R.P. Low platelet adhesiveness and other hemostatic abnormalities in hypothyroidism. *Ann Intern Med* 1975, **82**: 342–346.
- Hellem, A.J., Segard, E. & Solem, J.H. The adhesiveness of human blood platelets and thyroid function. *Acta Med Scand* 1975, **197**: 15–17.
- Nordoy, A., Vik-mo, H. & Berntsen, H. Haemostatic and lipid abnormalities in hypothyroidism. *Scand J Haematol* 1976, **16**: 154–160.
- Tudhope, G.R. Endocrine disorders. In: Israels, M.C.G. & Delamore, I.W. (eds) *Haematological Aspects of Systemic Disease*. W.B. Saunders, London, 1976, pp. 162–200.
- Endo, Y. Relationship between thyroid function and platelet counts. *Acta Haematol* 1985, **74**: 58–59.
- Ford, H.C. & Carter, J.M. Moderate, chronic hypothyroidism does not lead to more small-sized platelets in the circulation. *Thromb Haemost* 1988, **60**: 524.
- Stern, B. & Altschule, M.D. Hematological studies in hypothyroidism following total thyroidectomy. *J Clin Invest* 1936, **15**: 633–641.
- Sjoberg, R.J., Kidd, G.S., Swanson, E. *et al.* Thromboxane and prostacyclin generation in hypothyroidism. *Clin Res* 1984, **32**: 690A.
- Van Doormaal, J.J., van der Meer, J., Oosten, H.R., Halie, M.R. & Doorenbos, H. Hypothyroidism leads to more small-sized platelets in circulation. *Thromb Haemost* 1987, **58**: 964–965.
- Ford, H.C., Toomath, R.J., Carter, J.M., Delahunt, J.W. & Fagerstrom, J.N. Mean platelet volume is increased in hyperthyroidism. *Am J Hematol* 1988, **27**: 190–193.
- Savage, R.A. & Sipple, C. Marrow myxedema. *Arch Pathol Lab Med* 1987, **111**: 375–377.
- Gardikas, C., Arapakis, G. & Dervenagas, S. The effect of certain hormones on platelet aggregation *in vitro*. *Acta Haematol* 1972, **47**: 297–302.
- O'Regan, S. & Fong, J.S.C. Platelet hyperaggregability in hypothyroid rats. *Proc Soc Exp Biol Med* 1978, **158**: 575–577.
- Zeigler, Z.R., Hasiba, U., Lewis, J.H., Vagnucci, A.H., West, V.A. & Bezek, E.A. Hemostatic defects in response to aspirin challenge in hypothyroidism. *Am J Hematol* 1986, **23**: 391–399.
- Zeigler, Z., Hasiba, U., Lewis, J., Vagnucci, A., West, V. & Bezek, E. Exaggeration of defective platelet function by methyl dopa in hypothyroidism. *Am J Hematol* 1984, **17**: 209–215.
- Ingbar, S.H. The thyroid gland. In: Wilson, J.D. & Foster, D.W. (eds) *Williams Textbook of Endocrinology*, 7th edition. W.B. Saunders, Philadelphia, 1985, pp. 682–815.
- Thomson, J.A. Alterations in capillary fragility in thyroid disease. *Clin Sci* 1964, **26**: 55–60.
- Tachman, M.L. & Guthrie, G.P. Jr. Hypothyroidism: diversity of presentation. *Endocr Rev* 1984, **5**: 456–465.
- Dalton, R.G., Savidge, G.F., Matthews, K.B. *et al.* Hypothyroidism as a cause of acquired von Willebrand's disease. *Lancet* 1987, **i**: 1007–1009.
- Jackson, A.S. Acute hemorrhagic purpura associated with exophthalmic goiter. *JAMA* 1931, **96**: 38–39.
- Crabtree, G.R., Lee, J.C. & Cornwell, G.G. III. Autoimmune thrombocytopenia purpura and Hashimoto's thyroiditis. *Ann Intern Med* 1975, **83**: 371–372.
- Ardeman, S., Boralessa, H. & Sale, R.F. Coagulation inhibitor in hypothyroidism. *Br Med J* 1981, **282**: 1508.
- Valdemarsson, S., Fagher, B., Hedner, P., Monti, M. & Nilsson-Ehle, P. Platelet and adipocyte thermogenesis in hypothyroid patients: a microcalorimetric study. *Acta Endocrinol* 1985, **108**: 361–366.
- Hymes, K., Blum, M., Lackner, H. & Karpatkin, S. Easy bruising, thrombocytopenia, and elevated platelet immunoglobulin G in Graves' disease and Hashimoto's thyroiditis. *Ann Intern Med* 1981, **94**: 27–30.
- Egeberg, O. Influence of thyroid function on the blood clotting system. *Scand J Clin Lab Invest* 1963, **15**: 1–7.
- Abildgaard, C.F., Suzuki, Z., Harrison, J., Jefcoat, K. & Zimmerman, T.S. Serial studies in von Willebrand's disease: variability versus 'variants'. *Blood* 1980, **56**: 712–716.
- Loelinger, E.A., van der Esch, B., Mattern, M.J. & Hemker, H.C. The biological disappearance rate of prothrombin, Factors VII, IX and X from plasma in hypothyroidism, hyperthyroidism, and during fever. *Thromb Diath Haem* 1964, **10**: 267–277.
- Shenfield, G.M. Influence of thyroid dysfunction on drug pharmacokinetics. *Clin Pharmacokinet* 1981, **6**: 275–297.
- Walters, M.B. The relationship between thyroid function and anticoagulant therapy. *Am J Cardiol* 1963, **11**: 112–114.
- Ingram, G.I.C. Increase in antihemophilic globulin activity following infusions of adrenaline. *J Physiol* 1961, **156**: 217–224.
- Egeberg, O. Changes in activity of antihemophilic A factor (F.VIII) and in bleeding time associated with muscular exercise and adrenalin infusions. *Scand J Clin Lab Invest* 1962, **14**: 471–474.
- Landsberg, L. & Young, J.B. Catecholamines and the sympathoadrenal system: In: Ingbar, S.H. & Braverman, L.E. (eds) *The Thyroid*, 5th edition. J.B. Lippincott, Philadelphia, 1986, pp. 910–919.
- Rogers, J.S. II & Shane, S.R. Factor VIII activity in normal volunteers receiving oral thyroid hormone. *J Lab Clin Med* 1983, **102**: 444–449.
- Tuddenham, E.G.D., Lazarchick, J. & Hoyer, L.W. Synthesis and release of factor VIII by cultured human endothelial cells. *Br J Haematol* 1981, **47**: 617–626.
- Crispell, K.R., Parson, W. & Hollifield, G. A study of the rate of protein synthesis before and during the administration of L-triiodothyronine to patients with myxedema and healthy volunteers using N-15 glycine. *J Clin Invest* 1956, **35**: 164–169.
- Hume, R. Fibrinolytic activity and thyroid function. *Br Med J* 1965, **1**: 686–688.
- Rennie, J.A.N., Bewsher, P.D., Murchison, L.E. & Ogston, D. Coagulation and fibrinolysis in thyroid disease. *Acta Haematol* 1978, **58**: 171–177.
- Bennett, N.B., Ogston, C.M. & McAndrew, G.M. The thyroid and fibrinolysis. *Br Med J* 1967, **4**: 147–148.
- Farid, N.R., Griffiths, B.L., Collins, J.R., Marshall, W.H. & Ingram, D.W. Blood coagulation and fibrinolysis in thyroid disease. *Thromb Haemost* 1976, **35**: 415–422.
- Simone, J.V., Abildgaard, C.F. & Schulman, I. Blood coagulation in thyroid dysfunction. *N Engl J Med* 1965, **273**: 1057–1061.
- Landsberg, L. & Young, J.B. Catecholamines and the sympathoadrenal system. In: Ingbar, S.H. & Braverman, L.E. (eds) *The Thyroid*, 5th edition. J.B. Lippincott, Philadelphia, 1986, pp. 1192–1193.
- Weinberg, A.D., Brennan, M.D. Gorman, C.A., Marsh, H.M. & O'Fallon, W.M. Outcome of anesthesia and surgery in hypothyroid patients. *Arch Intern Med* 1983, **143**: 893–897.
- Ladenson, P.W., Levin, A.A., Ridgway, E.C. & Daniels, G.H. Complications of surgery in hypothyroid patients. *Am J Med* 1984, **77**: 261–266.

48. Orr, F.R. Haemorrhage in myxoedema coma. *Lancet* 1962, ii: 1012–1015.
49. Feldman, J.M. & Roche, J. Effect of hyper- and hypothyroidism on platelet monoamine oxidase activity and serotonin metabolism. *Metabolism* 1977, 26: 657–664.
50. Rogers, J.S.II, Shane, S.R. & Jencks, F.S. Factor VIII activity and thyroid function. *Ann Intern Med* 1982, 97: 713–716.