Disorders of Hemostasis • Research Paper

# High prevalence of acquired von Willebrand's syndrome in patients with thyroid diseases undergoing thyroid surgery

[haematologica]
2004;89:1341-1346

MASSIMO FRANCHINI
CHIARA ZUGNI
DINO VENERI
GIORGIO GANDINI
GIUSEPPE LIPPI
FRANCO MANZATO
PAOLO BRAZZAROLA

A B S T R A C T

**Background and Objectives.** Various coagulation abnormalities occur in patients with thyroid diseases. These abnormalities range from subclinical laboratory findings to hemorrhage or thromboembolism. However, the prevalence of hemostatic abnormalities in patients with thyroid diseases is still unclear.

**Design and Methods.** Between January 1999 and December 2003, 1342 consecutive patients with various thyroid diseases who were candidates for thyroid surgery underwent preoperative screening of hemostatic parameters including prothrombin time, activated partial thromboplastin time and platelet-related hemostasis with the PFA-100 platelet-function analyzer.

**Results.** Thirty-nine patients (2.9%) had abnormalities of the coagulation screening tests. Of these, 35 patients had von Willebrand's disease (type 1 in 33 cases and type 2A in 2 cases), 2 patients had decreased platelet aggregability, and 2 patients had coagulation factor XI deficiency. As all patients with coagulation abnormalities responded to subcutaneous desmopressin injection (0.3 μg/kg BW), this drug was successfully used as surgical prophylaxis.

**Interpretation and Conclusions.** Up to 3% of patients with thyroid diseases undergoing thyroid surgery have coagulation abnormalities, in most cases resembling von Willebrand's disease. Coagulation screening tests are needed in order to identify those patients at increased risk of bleeding.

Key words: von Willebrand factor, acquired, bleeding, thyroid, surgery.

*From the Servizio di Immunoematologia e Trasfusione, Centro Emofilia, Azienda Ospedaliera di Verona, Verona; Dipartimento di Chirurgia, Chirurgia Generale B, Università di Verona, Verona; Dipartimento di Medicina Clinica e Sperimentale, Sezione di Ematologia, Università di Verona; Istituto di Chimica e Microscopia Clinica, Dipartimento di Scienze Biomediche e Morfologiche, Università di Verona, Verona; Laboratorio di Analisi Chimico-Cliniche, Ospedale C. Poma, Mantova, Italy.*

*Correspondence: Massimo Franchini, MD, Servizio di Immunoematologia e Trasfusione, Centro Emofilia, Ospedale Policlinico, Piazzale Ludovico Scuro, 37134 Verona, Italy. E-mail: massimo.franchini@mail.azosp.vr.it*





Various acquired abnormalities of coagulation have been reported in patients with thyroid dysfunction.[1-5] These abnormalities range from subclinical laboratory findings to clinically significant coagulopathies and, more rarely, major hemorrhagic or thromboembolic complications.[6] Although the matter is still controversial, it seems that patients with hypothyroidism have a bleeding tendency[7-12] whereas patients with hyperthyroidism are at risk of thromboembolic events.[13-15] Moreover, since the thyroid gland is a richly vascularized organ, the risk of bleeding may be particularly enhanced in those patients with thyroid diseases undergoing thyroid surgery.[16]

Considering the fact that personal or family history of bleeding is usually negative in patients with acquired hemostatic defects, we decided to screen 1342 consecutive patients with various thyroid diseases who were scheduled for thyroid surgery for the most important parameters of hemostasis (platelet function for primary hemostasis and prothrombin time and activated partial thromboplastin time for secondary hemostasis) in order to assess their bleeding tendency.

## Design and Methods

### *Patients and study design*

Between January 1999 and December 2003, 1342 consecutive patients with thyroid diseases listed for thyroid surgery were seen at the University Hospital of Verona. All these patients underwent preoperative coagulation screening tests, including the activated partial thromboplastin time (APTT), prothrombin time (PT) and closure

time measured by the PFA-100 platelet function analyzer. Acetylsalicylic acid and non-steroidal anti-inflammatory drugs were stopped at least one week before the *in vitro* evaluation of platelet function. All abnormal coagulation parameters were confirmed by repeat testing on a new blood sample. All patients were euthyroid at the time the coagulation screening was carried out. When a coagulation screening test abnormality was detected, additional coagulation tests were performed (i.e., von Willebrand factor antigen [VWF:Ag], ristocetin cofactor [VWF:RCo] levels and/or coagulation factors levels and/or platelet aggregation) in order to characterize the hemostatic defect. In determining the type of von Willebrand's disease (VWD), we adhered to the guidelines of the Italian Association of Hemophilia Centers (AICE).17 In fact, in the case of a VWF:RCo/Ag ratio > 0.7, type 1 VWD was diagnosed; in the case of VWF:RCo/Ag ratio < 0.7, type 2 VWD was diagnosed. To characterize type 2 VWD further, ristocetin-induced platelet agglutination (RIPA) testing was required: when RIPA was increased, type 2B VWD was diagnosed, whereas when RIPA was decresased, type 2A or 2M was diagnosed according to the absence or presence of high molecular weight VWF multimers.

All patients were questioned about a personal and family history of blood coagulation disorders. In those patients with abnormal hemostatic parameters, coagulation screening tests of first degree relatives was also performed. Before surgery, the patients with hemostatic defects were tested for their response to a subcutaneously injected dose of 0.3 μg/kg of body weight of desmopressin (DDAVP) and the abnormal coagulation parameters were measured before and 120 minutes after the DDAVP injection. If there was a good response to the preoperative DDAVP test, subcutaneous desmopressin was used as surgical prophylaxis at a dosage of 0.3 μg/kg BW daily for 3-5 consecutive days starting 1 hour before the operation. We also documented any bleeding episodes during or after surgery and adverse drug reactions possibly occurring in association with the treatment. Treatment outcome was rated as excellent (achievement of normal hemostasis), good (mildly abnormal hemostasis not requiring additional therapy), or poor (hemostasis less than expected) as a measure of overall efficacy. The patients with hemostatic abnormalities before surgery were re-evaluated 3 and 6 months postoperatively, and new blood samples were collected in order to repeat the coagulation screening tests.

### *Laboratory analysis*

Prothrombin time measurements were performed on a Behring Coagulation System (BCS, Dade Behring, Marburg, Germany), employing human thromboplastin Thromborel, ISI 1.07 (Dade Behring) and results were finally converted into an international normalized ratio (INR). Activated partial thromboplastin time measurements were performed in duplicate on a Behring Coagulation Timer (BCT, Dade Behring) employing Pathromptin SL (micronized silica + calcium chloride solution, Dade Behring). The assay was performed according to the instructions provided by the manufacturer. The activities of clotting factors VIII (FVIII:C) and XI (FXI:C) were measured on the BCT using a modification of the one-stage APTT test (Behring Diagnostic GmbH, Marburg, Germany). All measurements were performed in duplicate in the same analytical session and the results were referred to a reference standard curve obtained by serial dilutions of standard human plasma (Behring) mixed with each respective deficient plasma. Results of duplicate tests were averaged and then expressed in terms of factor activity (%). von Willebrand factor antigen (VWF:Ag) was measured by a commercial automated enzyme-linked immunosorbent assay on a mini Vidas analyzer (bioMerieux, Marcy-l'Etoile, France); von Willebrand factor activity (WF:RCo) was assessed on a BCT (Dade Behring) by a platelet agglutination method.

The PFA-100 analyzer (Dade Behring) uses a disposable cartridge in which the internal active membrane is coated with either collagen-ADP (CADP) or collagen-epinephrine (CEPI). The interaction of whole anticoagulated blood with the agonists, in a condition of high shear rates, triggers platelet activation and the resulting formation of a stable platelet plug arrests the flow of the blood. The response of the sample is recorded as the time required to reach full occlusion and is expressed as a closure time (CT). Ristocetin-induced platelet agglutination (RIPA) was measured by mixing different concentrations of ristocetin and patient platelet-rich plasma (PRP) in an aggregometer. Results are expressed as the concentrations of ristocetin (mg/mL) able to induce 30% of agglutination. Multimeric analysis of plasma VWF was performed by low-resolution sodium dodecyl sulphate-agarose gel electrophoresis using a discontinuous buffer system. For the platelet aggregation studies, venous blood samples (40 mL) were collected by venipuncture into 1:10 volume trisodium citrate (3.2% wt/vol) from patients who had not been taking any anti-platelet drugs during the previous 3 weeks. Platelet-rich plasma was obtained by centrifugation at 700g for 15 minutes. Samples were kept at room temperature and used for the tests within 2 hours. Platelet-rich plasma was maintained in the aggregometer at 37°C for 1 minute in HEPES buffer in the presence of 1 mmol/L $CaCl_2$ and 1 mmol/L $MgSO_4$, with continuous stirring at 1000 rpm and was then stimulated with the agonists. The rate of platelet aggregation was monitored for 3

**Table 1. Base-line characteristics of the 1342 patients included in the study.**

| *Characteristic* | *Value* |
|---|---|
| Median age (range), years | 51 (17-81) |
| Sex, M/F | 268/1074 |
| Type of thyroid disease | |
| Multinodular goiter | 856 |
| Uninodular goiter | 20 |
| Graves' disease | 101 |
| Plummer's disease | 34 |
| Hashimoto's thyroiditis | 10 |
| Subacute lymphocytic thyroiditis | 10 |
| Adenoma | 75 |
| Papillary carcinoma | 173 |
| Follicular carcinoma | 32 |
| Medullary carcinoma | 12 |
| Anaplastic carcinoma | 1 |
| Hurtle cell neoplasm | 18 |

minutes after the addition of the agonist using a 4-channel aggregometer (Aggrecorder II, PA-3220; Daiichi); the rate was measured as the change in percentage of transmitted light according to Born.

### *Statistical analysis*

We used the Student t-test for analysis of normally distributed continuous data and the $\chi^2$ or Fisher's exact test for analysis of categorical data. A $p$ value <0.05 was considered statistically significant.

## Results

### *Patients*

Table 1 shows the baseline characteristics of the 1342 patients included in the study. The median age of this series was 51 years and 80% of the patients were women. Three hundred and eleven patients (23.2%) underwent thyroid surgery for a thyroid neoplasm. As regards the operation, 942 patients (70.2%) underwent total thyroidectomy, 315 (23.4%) hemithyroidectomy, 72 (5.4%) subtotal thyroidectomy, and 13 (1%) a local excision. In 69 cases (5.1%) the surgical procedure was a reoperation (totalization); parathyroidectomy and lymphadenectomy were associated in 48 cases (3.6%) and 53 cases (3.9%), respectively.

### *Prevalence of coagulation abnormalities*

Table 2 presents the coagulation abnormalities found preoperatively during the coagulation screening tests. Thirty-nine patients (2.9%) had abnormalities of these screening tests. Twenty-six patients (1.9%) had a prolonged APTT and raised PFA-100 values, whereas of the remaining 13 patients, 11 patients (0.9%) had only

**Table 2. Results of the coagulation abnormalities found during the preoperative coagulation screening tests.**

| *Tests* | *Number of patients** | *Results†* |
|---|---|---|
| APTT (ratio) | 28 (2.1) | 1.34±0.1 |
| Closure time (PFA-100) | | |
| CADP (seconds) | 33 (2.1) | 136.4±26.7 |
| CEPI (seconds) | 37 (2.8) | 168.3±33.3 |

*APTT: activated partial thromboplastin time; PFA: platelet function analyzer; CADP: collagen ADP; CEPI: collagen epinephrine. Normal values. APTT (ratio): 0.85-1.17; CT-ADP: <110 seconds; CT-EPI: <140 seconds.*
**Number (percentage); † means ±SD.*

**Table 3. Laboratory characteristics of the 35 patients with von Willebrand's disease at baseline and 2 hours after subcutaneous desmopressin injection (0.3 μg/kg).**

| *Parameters* | *Normal values* | *Baseline** | *2 hours after DDAVP** |
|---|---|---|---|
| APTT (ratio) | 0.85-1.17 | 1.29±0.1 | 1.05±0.1 |
| VWF:Ag | 60-150% | 42.6±8.2 | 121.3±26.8 |
| VWF:RCo | 50-150% | 44.1±9.5 | 119.7±21.1 |
| FVIII:C | 50-150% | 51.1±12.4 | 153.4±18.8 |
| Closure time (PFA-100) | | | |
| CADP (seconds) | < 110 | 136.3±26.6 | 67.4±22.5 |
| CEPI (seconds) | < 140 | 168.2±33.3 | 88.2±19.9 |

*APTT: activated partial thromboplastin time; VWF:Ag: von Willebrand factor antigen; VWF:Rco: von Willebrand factor ristocetin cofactor; FVIII:C: coagulant factor VIII; PFA: platelet function analyzer; CADP: collagen ADP; CEPI: collagen epinephrine. *means ±SD.*

increased PFA-100 values and 2 patients (0.1%) had only increased APTT values. Additional coagulation tests allowed a diagnosis of von Willebrand's disease in 35 cases (type 1 in 33 cases and type 2a in 2 cases), decreased platelet aggregability in 2 cases (weak aggregation response to ADP), and decreased levels of coagulation factor XI in 2 cases (FXI:C levels of 42% and 40%; normal values 50-150%). The laboratory characteristics of the 35 VWD patients are reported in Table 3. The results did not differ in patients with 0 and non-0 blood types. As regards the primary thyroid disease, 34 out of the 39 patients with coagulation abnormalities had a multinodular goiter, 2 had Grave's disease, 2 had papillary cancer and 1 had medullary cancer. Thus, the association between the hemostatic defect and multinodular goiter (34/823, 4.1%) was 4 times higher than the association between coagulation abnormalities and other thyroid diseases (5/519, 1.0%, $p < 0.01$).

### *Surgical prophylaxis*

As all patients with hemostatic alterations responded to subcutaneous desmopressin, this drug was used as surgical prophylaxis in our patients (median days of treatment: 3.3, range 3-5 days). The response to subcutaneous DDAVP of the 35 patients with VWD is

reported in Table 3. As regards the 2 patients with platelet hypoaggregability, the DDAVP injection normalized the closure time determined by the platelet-function analyzer. Similarly, subcutaneous desmopressin increased the levels of FXI:C (from 42% and 40% to 53% and 55%, respectively) and normalized APTT (from 1.34 and 1.25 to 1.08 and 0.91, respectively) in the 2 patients with factor XI deficiency. No patient with coagulation abnormalities was transfused with blood components or derivatives during surgery or the postoperative period. The administration of DDAVP was well tolerated and no adverse drug reactions or thrombotic episodes were observed following injection of the drug. Prophylaxis was rated as excellent/good in all procedures.

### *Family screening and follow-up*

Six of the 39 patients with coagulation abnormalities had a personal history of prior hemorrhages (4 patients with von Willebrand's disease and 2 patients with coagulation factor XI deficiency), whereas 4 had a positive family history of bleeding (2 patients with von Willebrand's disease and 2 patients with coagulation factor XI deficiency). Coagulation tests of the relatives of these 39 patients revealed that 5 family groups had the same coagulation defect as that of the probands (3 with von Willebrand's disease and 2 with coagulation FXI deficiency). Laboratory checks performed 3 and 6 months after surgery showed that coagulation parameters had normalized in 32 out of the 35 patients with von Willebrand's disease and in the 2 patients with abnormal platelet aggregation. Coagulation abnormalities did however persist in the remaining 3 cases of von Willebrand's disease and in the 2 patients with FXI deficiency (in all these patients the same coagulation defect was detected in their relatives). Thus, we conclude that 34 patients had an acquired hemostatic defect (30 VWD type 1, 2 VWD type 2A and 2 platelet hypoaggregability), whereas 5 patients had an hereditary defect (3 VWD type 1 and 2 heterozygous FXI deficiency).

## Discussion

It is well known that various coagulation abnormalities occur in patients with thyroid diseases, these abnormalities ranging from subclinical laboratory findings to hemorrhage or thromboembolism.[1-4] The coagulation abnormalities in patients with thyroid deficiency are varied,[7,8] but frequently the coagulopathy consists of a defect of primary hemostasis which results in a bleeding tendency that is usually mild (e.g. nose or gingival bleeding, menorrhagia, easy bruising), but which can, rarely, be severe (e.g. hemorrhages following trauma or surgery).[4] Coagulation tests in patients with thyroid hormone deficiency usually show prolongation of the APTT and a normal or slightly shortened PT, reflecting the abnormalities of the related coagulation factors.[18-21] That hypothyroidism is associated with depression of a variety of coagulation factors was first observed by Egeberg[1] and Simone[2] who found a significant decrease of factor VIII, IX and XI levels in hypothyroid patients. The latter author also observed that thyroid hormone therapy produced a positive response in antihemophilic-factor activity (FVIII:C). Other studies confirmed these findings and also described low levels of plasma coagulation factors VII, X and XII.[2,7,22]

As regards primary hemostasis, there are reports of qualitative platelet abnormalities in patients with thyroid hormone deficiency.[23-26] Palareti and colleagues[26] studied 21 patients with acquired hypothyroidism after total thyroidectomy and found impaired platelet reactivity not only to ristocetin but also to collagen and epinephrine; this impairment was completely corrected by replacement therapy with L-thyroxine. Myrup and colleagues[3] studied primary hemostasis in hyperthyroid and hypothyroid patients and, among the parameters analyzed (bleeding time, platelet count, $\beta_2$-macroglobulin, fibrinogen, fibronectin, platelet aggregation and agglutination), they found a significantly longer bleeding time, an impaired agglutination response to ristocetin and greater platelet aggregation in response to ADP in untreated hypothyroid patients than in normal controls. Moreover, the authors found that the levels of von Willebrand factor antigen in plasma from hypothyroid patients were less than half those recorded in hyperthyroid patients. Bleeding time, ristocetin-induced platelet agglutination and VWF:Ag normalized during L-thyroxine treatment, suggesting that the prolonged primary hemostasis in hypothyroidism is a consequence of thyroid hormone status.

Similar results were reported by Rogers and colleagues,[27,28] who found decreased levels of factor VIII coagulant activity, VWF:Ag and ristocetin co-factor activity (VWF:RCo) in 5 of 21 (24%) untreated hypothyroid patients; these abnormalities reversed after hormone replacement therapy.

Abnormalities of primary hemostasis resembling acquired VWD are the most frequent coagulation disorder observed in hypothyroidism.[10-12,29-37] The presenting symptoms are easy bruising, epistaxis and mucosal bleeding. Hemostatic tests show a prolonged bleeding time and decreased FVIII:C, VWF:Ag and VWF:RCo levels, whereas multimeric analysis reveals a pattern of type 1 or type 2 VWD.[33] However, the diagnosis of this associated coagulopathy is very difficult since it is usually not detected by routine laboratory tests and hypo-

thyroidism often has an insidious onset with subtle clinical signs and symptoms. Thus, the correct diagnosis is frequently not established until the bleeding tendency is manifested by major hemorrhage following trauma or surgery. However, the majority of studies report that acquired VWD associated with hypothyroidism resolves completely after thyroid hormone therapy.

The pathogenesis of hypothyroidism-associated acquired VWD, although still unclear, seems to be quite different from that of VWD associated with other pathologies (e.g. hematologic malignancies) characterized by the development of a specific anti-VWF antibody that binds to VWF thus forming an immune complex which is rapidly cleared from the circulation by the reticuloendothelial system. In hypothyroidism, the pathogenic mechanism most frequently advocated by various authors is a decrease of VWF protein synthesis in the absence of adequate levels of thyroxine.[3] The reversal of VWD following thyroid hormone replacement could be the result of two effects: an increased release of VWF from endothelial cells due to increased sensitivity to epinephrine after thyroid hormone therapy and a non-specific stimulation of hepatic protein synthesis by thyroid hormone.

Our study, in which we found abnormalities of primary hemostasis (platelet hypoaggregability and reduced levels of von Willebrand factor) in patients with various thyroid diseases, confirms previous findings from other authors. However, as these hemostatic abnormalities were observed in patients with a normal hormone thyroid status, a different pathogenic mechanism is presumably involved. While patients with hyperthyroidism seem to have an increased risk of thromboembolic complications[3,38-41] a hemorrhagic risk has been observed in those with thyroid cancers. In fact, Rosen and colleagues[42] found an association between factor XI deficiency and thyroid neoplasia and, in a previous study, we reported on two patients with localized thyroid cancer (one patient with medullary and another with papillary thyroid cancer) and acquired VWD who underwent thyroidectomy with desmopressin as surgical prophylaxis.[16]

The great majority of the coagulation abnormalities found in the present study resembled an acquired von Willebrand's syndrome, as documented by the normalization of VWF after surgery. Although most of the abnormalities occurred in patients with multinodular goiter, hemostatic defects were also observed in patients with other thyroid diseases. All the patients with coagulation abnormalities were managed effectively with desmopressin and there were no hemorrhagic complications during or after surgery in any of the patients. Interestingly, the 2 patients with a heterozygous FXI deficiency also responded to desmopressin, thus confirming previous reports by us[43] and other investigators.[44]

Moreover, the lack of surgery-related bleeding events in the other patients with normal coagulation tests documents the high sensitivity of this screening method and compares favorably with the data reported in literature on similar series of patients.[45,46]

Since up to 3% of patients with thyroid diseases requiring surgery may have acquired hemostatic abnormalities, we advise preoperative coagulation screening tests in order to identify those patients with an increased risk of bleeding.

*MF, DV and PB designed the study; MF, GG and DV wrote the manuscript; CZ and PB collected the data; GL and FM were responsible for coagulation test analysis.*

*The authors reported no potential conflitcs of interest.*

*Manuscript received May 25, 2004. Accepted August 16, 2004.*



## References

1. Egeberg BO. Influence of thyroid function on the blood clotting system. Scand J Clin Lab Invest 1963;15:1-7.
2. Simone JV, Abildgaard CF, Schulman I. Blood coagulation in thyroid dysfunction. N Engl J Med 1965;273:1057-61.
3. Myrup B, Bregengård C, Faber J. Primary haemostasis and thyroid disease. J Int Med 1995;238:59-63.
4. Hofbauer LC, Heufelder AE. Coagulation disorders in thyroid diseases. Eur J Endocrinol 1997;136:1-7.
5. Rennie JA, Bewsher PD, Murchison LE, Ogston E. Coagulation and fibrinolysis in thyroid disease. Acta Haematol 1978; 58:171-7.
6. Farid NR, Griffiths BL, Collins JR, Marshall WH, Ingram DW. Blood coagulation and fibrinolysis in thyroid disease. Thromb Haemost 1976;35:415-22.
7. Ford HC, Carter JM. Haemostasis in hypothyroidism. Postgrad Med J 1990; 66:280-4.
8. Erem C, Kavgaci H, Ersöz H, Hacihasanoglu A, Ukinc K, Karti SS, et al. Blood coagulation and fibrinolytic activity in hypothyroidism. Int J Clin Pract 2003; 57:78-81.
9. Edson JR, Fecher DR, Doe RP. Low platelet adhesiveness and other abnormalities in hypothyroidism. Ann Intern Med 1975;82:342-6.
10. Dalton RG, Dewar MS, Savidge GF, Kernoff PB, Matthews KB, Greaves M, et al. Hypothyroidism as a cause of acquired von Willebrand's disease. Lancet 1987; 1:1007-9.
11. Smith SR, Anger MJ. Hypothyroidism and von Willebrand's disease. Lancet 1987; 1:1314.
12. Attivissimo LA, Lichtman SM, Klein I. Acquired von Willebrand's syndrome causing a hemorrhagic diathesis in a patient with hypothyroidism. Thyroid 1995; 5:399-401.
13. Marongiu F, Conti M, Murtas ML, Mameli G, Sorano GG, Martino E. Activation of blood coagulation in Graves' disease. Horm Metab Res 1991;23:609-11.
14. Erem C, Ersöz H, Karti SS, Ukinc K, Hacihasanoglu A, Deger O, et al. Blood coagulation and fibrinolysis in patients with hyperthyroidism. J Endocrinol Invest 2002;25:345-50.
15. Hofbauer LC, Spitzweg C, Heufelder AE. Graves' disease associated with the primary antiphospholipid syndrome. J Rheumatol 1996;23:1435-7.
16. Franchini M, de Gironcoli M, Lippi G, Manzato F, Brazzarola P, Bottura D, et al. Efficacy of desmopressin as surgical prophylaxis in patients with acquired von Willebrand disease undergoing thyroid surgery. Haemophilia 2002;8:142-4.
17. Federici AB, Castaman G, Mannucci PM. Guidelines for the diagnosis and management of von Willebrand disease in Italy. Haemophilia 2002;8:607-21.
18. Graninger W, Pirich KR, Speiser W, Deutsch E, Waldhäusl WK. Effect of thyroid hormones on plasma protein concentration in man. J Clin Endocrinol Metab 1986;63:407-11.

19. Erfuth EM, Ericsson UB, Egervall K, Lethagen SR. Effect of desmopressin and long-term thyroxine replacement on haemostasis in hypothyroidism. Clin Endocrinol (Oxf) 1995;42:373-8.
20. Van Oosterom AT, Kerkhoven P, Veltkamp JJ. Metabolism of the coagulation factors of the prothrombin complex in hypothyroidism in man. Thromb Haemost 1979;41:273-85.
21. De Feo P. Hormonal regulation of human protein metabolism. Eur J Endocrinol 1996;135:7-18.
22. Nordoy A, Vikmo H, Berntsen H. Haemostatic and lipid abnormalities in hypothyroidism. Scand J Haematol 1976; 16: 154-60.
23. Zeigler ZR, Hasiba U, Lewis JH, Vagnucci AH, West VA, Bezek EA. Hemostatic defects in response to aspirin challenge in hypothyroidism. Am J Hematol 1986; 17:209-15.
24. Hellem AJ, Segaard E, Solem JH. The adhesiveness of human blood platelets and thyroid function. Acta Med Scand 1975;197:15-7.
25. Edson JR, Fecher DR, Doe RP. Low platelet adhesiveness and other abnormalities in hypothyroidism. Ann Intern Med 1975; 82:342-6.
26. Palareti G, Biagi G, Legnani C, Bianchi D, Serra D, Savini R, et al. Association of reduced factor VIII with impaired platelet reactivity to adrenalin and collagen after total thyroidectomy. Thromb Haemost 1989;62:1053-6.
27. Rogers JS, Shane SR, Jencks FS. Factor VIII activity and thyroid function. Ann Intern Med 1982;97:713-6.
28. Rogers JS, Shane SR. Factor VIII activity in normal volunteers receiving oral thyroid hormone. J Lab Clin Med 1983; 102: 444-9.
29. MacCallum PK, Rodgers M, Taberner DA. Hypothyroidism and von Willebrand's disease. Lancet 1987;1:1314.
30. Thornton JG, Parapia LA, Minford AMB. Hypothyroidism and von Willebrand's disease. Lancet 1987;1:1314-5.
31. Nitu-Whalley IC, Lee CA. Acquired von Willebrand syndrome - report of 10 cases and review of the literature. Haemophilia 1999;5:318-26.
32. Michiels JJ, Schroyens W, Berneman Z, van der Planken M. Acquired von Willebrand syndrome type 1 in hypothyroidism: reversal after treatment with thyroxine. Clin Appl Thromb Hemost 2001;7:113-5.
33. Blesing NE, Hambley H, McDonald GA. Acquired von Willebrand's disease and hypothyroidism: report of a case presenting with menorrhagia. Postgrad Med J 1990;66:474-6.
34. Bruggers CS, McElligott K, Rallison ML. Acquired von Willebrand disease in twins with autoimmune hypothyroidism: response to desmopressin and L-thyroxine therapy. J Paed 1994; 125: 911-3.
35. Rinder MR, Richard RE, Rinder HM. Acquired von Willebrand's disease: a concise review. Am J Hematol 1997; 54: 139-45.
36. Aylesworth C, Smallridge RC, Rick ME, Alving BM. Acquired von Willebrand's disease: a rare manifestation of postpartum thyroiditis. Am J Hematol 1995; 50:217-9.
37. Tjan-Heijnen VCG, Harthoorn-Lasthuizen EJ, Kurstjens RMA, Koolen MI. A patient with postpartum primary hypothyroidism and acquired von Willebrand's disease. Neth J Med 1994;44:91.
38. Liu L, Wang X, Lin Z, Wu H. Elevated plasma levels of vWF:ag in hyperthyroidism are mediated through beta-adrenergic receptors. Endocrine Res 1993;19:123-33.
39. Morishita E, Hashimoto T, Asakura H, Saito M, Yamazaki M, Aoshima K, et al. Increased plasma levels of free tissue factor pathway inhibitor in patients with Graves' disease. Thromb Haemost 1998;79:919-23.
40. Chadaverian R, Bruckert E, Giral P, Turpin G. Relationship between thyroid hormones and fibrinogen levels. Blood Coagul Fibrinol 1999;10:481-6.
41. Marongiu F, Conti M, Mameli G, Murtas ML, Balzano S, Sorano G, et al. Fibrinogen and fibrinolytic activity in hyperthyroidism before and after antithyroid treatment. J Endocrinol Invest 1988; 11: 723-5.
42. Rosen IB, Anderson I, Musclow CE. The factor of factor XI deficiency in thyroid neoplasia. Surgery 1986;100:1062-7.
43. Franchini M, de Gironcoli M, Lippi G, Manzato F, Aprili G, Gandini G. Prophylactic use of desmopressin in surgery of six patients with symptomatic heterozygous factor XI deficiency. Haematologica 2000;85:106-7.
44. Castaman G, Ruggeri M, Rodeghiero F. Clinical usefulness of desmopressin for prevention of surgical bleeding in patients with symptomatic heterozygous factor XI deficiency. Br J Haematol 1996;94:168-70.
45. Bellantone R, Lombardi CP, Bossola M, Boscherini M, De Crea C, Alesina P, et al. Total thyroidectomy for management of benign thyroid disease: review of 526 cases. World J Surg 2002;26:1468-71.
46. Zambudio AR, Rodriguez J, Riquelme J, Soria T, Canteras M, Parrilla P. Prospective study of postoperative complications after total thyroidectomy for multinodular goiters by surgeons with experience in endocrine surgery. Ann Surg 2004;240:18-25.