Thyroid dysfunction: effects on coagulation and fibrinolysis

Cedric Hermans, MD, MRCP(UK), PhD

Haemostasis and Thrombosis Unit
Division of Haematology
Cliniques universitaires Saint-Luc
1200 Brussels - BELGIUM
E-mail: hermans@sang.ucl.ac.be
Tel: 02-764-1785
Clinical case: 23-year-old woman

- Epistaxis
- Menorrhagia
- Bleeding post-dental extraction

- APTT: 42 sec (24-34 sec)
- Prothrombin time, thrombin time and fibrinogen: normal values

- Bleeding time: prolonged
- PFA-100 (Platelet function analyzer): prolonged
- Von Willebrand Factor level: 35% (50-150%)
- FVIIIc: 45% (50-150%)
Clinical case: 23-year-old woman

- Full blood count: normal
- TSH: increased
- T4: reduced
- Antithyroid antibodies: +

- Initiation of replacement therapy with L-T4
- Correction of APTT, PFA-100, FVIII and VWF
- Resolution of bleeding symptoms

Acquired von willebrand disease secondary to hypothyroidism
Is there an association between hypothyroidism and bleeding tendency?
Basic principles of clot formation

Primary Haemostasis

Platelets aggregates

Blood coagulation

Fibrin clot

Endothelium

Adhesion

Release

Aggregation

TXA2

ADP

CLOT

Fibrinogen

Prothrombine

Thrombine

Xa

TF/FVIIa

TF = Tissue Factor
# Physiology of Haemostasis

<table>
<thead>
<tr>
<th>Primary Haemostasis</th>
<th>Secondary Haemostasis</th>
<th>Fibrinolysis</th>
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<tbody>
<tr>
<td>Vasoconstriction (immediate)</td>
<td>Activation of coagulation factors</td>
<td>Activation of fibrinolysis (minutes)</td>
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<td>Platelet adhesion (seconds)</td>
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<td>Clot lysis (hours)</td>
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<td>Platelet aggregation (minutes)</td>
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**Vascular injury**
Primary haemostasis

Inactive platelets

Adhesion

Activation

Aggregation

Endothelial cells

vWF

Collagen
Platelets

Collagen

Endothelium

1. Factor VIII binding

2. Platelet adhesion

3. Platelets aggregation

FVIIIc

Von Willebrand Factor
FVIII – von willebrand factor complex

FVIII ≠ vWF
Coagulation cascade

Thrombin

Fibrinogen → Fibrin
Coagulation cascade

Intrinsic

XII
XI
IX
VIII
VII

Extrinsic

Tissue Factor

X
V
II
Fg

Fibrin Clot
Revised model of the coagulation cascade

- Tissue Factor (TF)
- Factor VIIa
- (Co) Factors X, IX, V, VIII, XI
- Thrombin (IIa)
- Fibrinogen
- TF → FVIIa → FXa → FVa → Thrombin → Thrombus
Blood clot

Platelets

Fibrin, von Willebrand factor
Fibrinolysis

Physiological clearance of fibrin clots
Coagulation versus Fibrinolysis

Coagulation cascade:
- Fibrinogen → Fibrin → Thrombin

Fibrinolysis:
- Fibrin → FDPs → Plasmin

Clot formation
Clot dissolution
Evaluation of haemostasis

**Primary Haemostasis**
- Platelet count
- Platelet function
  - Bleeding time
  - PFA-100
  - Platelet aggregation studies
- Von Willebrand factor levels

**Secondary Haemostasis (coagulation cascade)**
- APTT
- Prothrombin Time
- Fibrinogen level
- Thrombin Time

**Fibrinolysis**
- Euglobulin Lysis Time
- D-Dimers
- RoTEM
Bleeding time *in vivo*

Normal value < 8 minutes
Bleeding time in vitro
Closure Time
PFA-100 (Platelet Function Analyzer 100)

Before
- cupule
- ouverture Ø 150 µm
- capillaire Ø 200 µm
- filtre + Epinephrine ou ADP
- membrane

After
- thrombus plaquettaire
Closure time (PFA-100)

« Temps de saignement in vitro »

Cedric Hermans - UCL
Platelet aggregation studies

PRP = platelet rich plasma

Agreggometry
37°C, agitation

Addition of aggregation inducer:
ADP, arachidonic acid, etc.

Platelets aggregation

Light transmission

Irreversible aggregation
Reversible aggregation
Thrombin
Time
Fibrin Clot

Coagulation cascade

Intrinsic

XII
XI
IX
VIII
VII

Extrinsic

Tissue Factor

PTT / INR

aPTT
TCA

APTT = activated partial thromboplastin time

Thrombin Time

Cedric Hermans - UCL
Thyroid dysfunction and coagulation

Hypothyroidism

Bleeding tendency

Hyperthyroidism

Hypercoagulability
Thyroïd dysfunction and effects on coagulation and fibrinolysis: a systematic review

J Clin Endocrinol Metab, 2007

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Total (%) | 7 (17.9) | 8 (20.5) | 24 (61.5) | 11 (28.2) | 19 (48.7) |

Ref, references; hypo, hypothyroidism; hyper, hyperthyroidism; sub, subclinical
### Overall coagulation and fibrinolytic changes in medium quality studies

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aPTT, activated partial thromboplastin time; PT, prothrombin time; f, factor; C, activity; Ag, antigen; vWF, von Willebrand factor; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; ↑, increased; ↓, decreased; =, non statistical significant difference

Thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review  
J Clin Endocrinol Metab, 2007
Impact of hypothyroidism severity on coagulation disturbances

Moderate Hypothyroidism

- Hypercoagulability
- Increased risk of thrombosis
  - Elevated FVII
  - Decreased fibrinolytic activity
  - Elevated homocystein

Severe Hypothyroidism

- Bleeding tendency
  - Reduction vWF-FVIII
  - Increased fibrinolytic activity
Hypothyroidism and coagulation disturbances

Primary Haemostasis
- Thrombocytopenia
- Altered platelet function
- Decreased vWF

Secondary Haemostasis (coagulation cascade)
- Reduction FVIII,
- Reduction FVII, FIX, FX, FXII (+ reduced clearance)

Fibrinolysis
- Increased activity
- Reduced activity

Vascular injury
Effect of thyroid dysfunction on VWF
VON WILLEBRAND DISEASE

**Congenital**
- 1% general population
- 1/10,000 (severe forms)
- Family history
- Life-long bleeding history

**Acquired**
- Rare
- Frequently auto-immune
- Hypothyroidism (found in 6.1% patients with VWD)
- No family bleeding history
Hyperthyroidism and coagulation disturbances

Primary Haemostasis
- Thrombocytopenia (metabolic>immune)
- Vasculopathy
- Increase vWF

Secondary Haemostasis (coagulation cascade)
- Increase FVIII, Fibrinogen, FIX
- Increase turnover
  - FII, FVII, FX

Fibrinolysis
- Impaired fibrinolysis (hypofibrinolysis)

Vascular injury

Bleeding symptoms associated with hypothyroidism

Primary Haemostasis
- Mucosal bleedings
- Menorrhagia
- Brusing
- Post-op bleeding

Secondary Haemostasis (coagulation cascade)
- Deep haematomas
- Post-op bleeding

Fibrinolysis
- Delayed bleeding

Do not forget
- No family history of bleeding disorder
- No life-long bleeding history
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<td>Extraction dentaire</td>
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<td>Non ou insignifiant</td>
<td>oui</td>
<td>Suture / hémostase locale</td>
<td>Transfusion</td>
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<tr>
<td>Chirurgie</td>
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<td>Non ou insignifiant</td>
<td>oui</td>
<td>Ré-intervention</td>
<td>Transfusion</td>
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<tr>
<td>Ménorragies</td>
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<td>Non ou insignifiant</td>
<td>oui</td>
<td>Consultation, pilule, fer</td>
<td>Chirurgie / transfusion</td>
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<tr>
<td>Hémorragie du post-partum</td>
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<td>Non ou insignifiant</td>
<td>Oui (substitution en fer)</td>
<td>Transfusion, curetag</td>
<td>Hystérectomie</td>
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<tr>
<td>Hématomes musculaires</td>
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<td>Non ou insignifiant</td>
<td>oui</td>
<td>Motif de consultation</td>
<td>Chirurgie / transfusion</td>
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<tr>
<td>Hémarthroses</td>
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<td>Non ou insignifiant</td>
<td>oui</td>
<td>Motif de consultation</td>
<td>Chirurgie / transfusion</td>
</tr>
</tbody>
</table>

En général, si score > 3 c/o hommes et > 5 c/o femmes, bilan?
Bleeding work-up in patients with hypothyroidism

Primary Haemostasis
- Platelet count
- Platelet function
  - PFA-100
  - Platelet aggregation studies
- Von Willebrand factor levels (antigen-activity)

Secondary Haemostasis (coagulation cascade)
- APTT
- Prothrombin Time
- Fibrinogen level
- Thrombin Time

Fibrinolysis
- Difficult to evaluate
  - ELT
  - RoTEM

Vascular injury
Thyroid surgery

- The thyroid gland is a richly vascularized organ.
- Patients with acquired hemostatic defects usually have a negative personal and family bleeding history.
- Up to 3% of patients with thyroid disease undergoing thyroid surgery have been found to have coagulation bleeding abnormalities.
- Pre-operative coagulation screening should include: full blood count, APTT, PFA-100, vWF levels.
- In case of VWF deficiency, treatment with DDAVP (0.3 μg/kg) and Tranexamic acid (Exacyl, 1 g 3x/day) is recommended.
Coagulation and endocrine disorders

- Hyperthyroidism
  - Hypercoagulable state
- Hypothyroidism
  - Hypocoagulable state
  - Acquired VWD
- Hyperprolactinaemia
  - ? Increased risk of thrombosis
- Hypercortisolism
  - Venous thrombosis
  - Elevation FVIII – PAI-1
- Hypocortisolism
  - Possible bleeding diathesis
  - Acute adrenal failure: suspect APS – adrenal vein thrombosis
- Growth hormone excess
  - Possible mild hypercoagulable state
Endocrine disorders and coagulation

- Hormones influence the haemostatic system

- Studies on the relation between the haemostatic system and endocrine dysfunction have important methodological limitations

- Well designed clinical studies are necessary to assess the clinical relevance of coagulation abnormalities in patients with endocrine disorders
When should endocrine disorder be suspected in patients with coagulopathy?

<table>
<thead>
<tr>
<th>Signs</th>
<th>Endocrine disorder</th>
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<tbody>
<tr>
<td>Bleeding and decreased VWF</td>
<td>Hypothyroïdism ?</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>Subclinical hypothyroïdism ?</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>Cushing disease ?</td>
</tr>
<tr>
<td></td>
<td>Hypothyroïdism ?</td>
</tr>
</tbody>
</table>
Various abnormalities of blood coagulation have been reported and are common in patients with thyroid dysfunction.

Patients with hypothyroidism have a bleeding tendency although the haemostatic profile depends on the severity of the disease.

Patients with hyperthyroidism are at risk of thrombo-embolic events.

Most coagulation abnormalities are due to direct action of thyroid hormones on the synthesis/release of various haemostatic factors.

Correction of the levels of thyroid hormones is accompanied by a correction of the haemostatic balance.
Conclusions

• Acquired von Willebrand disease should be suspected in all patients with hypothyroidism and bleeding symptoms

• Screening for coagulation disturbances is recommended before thyroïd surgery