HORMONES AND COAGULATION

Victor Gerdes
Internist Slotervaart Hospital and Academic Medical Center
Amsterdam
Overview

- Introduction
- Thyroid hormone
- Cortisol
- Prolactin
- Implications
VTE Risk Factors

Genetic:
- factor V Leiden, prothrombin mutation, antithrombin / protein C and protein S deficiencies

Acquired:
- Surgery
- Immobility
- Cancer
- Long haul flight
- Pregnancy
- Oral anticontraceptives
- Hormone replacement therapy
Hormones

- Production
- Circulating hormone
- Receptor
- Regulation
Known effects thyroid hormone

- Heart rythm
- Metabolism
- Bone
- Muscle
- Gut
- Nervous system
- Lipids
- Skin
Known effects thyroid hormone

- Heart rythm
- Metabolism
- Bone
- Muscle
- Gut
- Nervous system
- Lipids
- Skin
- Coagulation
The value of case reports

Case History

Thyrotoxicosis as a Predisposing Factor for Cerebral Venous Thrombosis

Hein J. Verberne,¹ Eric Fliers,¹ Mark F. Prummel,¹ Jan Stam,² Dees P. Brandjes,³ and Wilmar M. Wiersinga¹
Thyroid hormone and coagulation 2007

- Case reports, especially cerebral vein / sinus thrombosis
- Stroke and atrial fibrillation
- Effect on factor VIII and von Willebrand factor
  - Hyperthyroidism: high factor VIII and VWF
  - Hypothyroidism: acquired von Willebrand’s disease
- VTE risk?

Squizzato et al, JCEM 2007
VTE Risk: a pilot study

- Case-control study

- Problems
  - Only citrate plasma
  - Probably low percentage of hyperthyroidism
$\beta = 0.92 \quad p < 0.01$

$\beta = 0.99 \quad p < 0.01$

$\beta = 0.96 \quad p < 0.01$
Case control study

- Patients with suspicion of deep venous thrombosis
Results

Van Zaane et al. Blood 2010
MEGA-study

- **Aim:** Confirm previous results in larger case-control study (2177 cases and 2826 controls).

- **Difference with first study:** Blood drawn months after diagnosis (median 10 months) instead of at the time of diagnosis.

- **Extra analyses:** Risk overt hyperthyroidism. Relation FT4 and coagulation variables (in controls).
Main Results MEGA-studie

- Confirmation increasing VTE risk in normal range of FT4.
- Overt hyperthyroidism OR 15.9 (95% CI 2.0 – 124.9).
Healthy volunteers

- Controlled, randomized cross-over study
  Effect of supra-physiologic dosis thyroid hormone on coagulation parameters.

- Studie A: 16 persons, levothyroxin 0.3 mg/day during 14 days.

- Studie B: 12 persons, levothyroxin 0.45 mg/day or 0.6 mg/day during 14 days depending on body weight.

Van Zaane et al JTH 2011
<table>
<thead>
<tr>
<th>Parameter (reference range)</th>
<th>Baseline</th>
<th>Day 14</th>
<th>Relative change (%)</th>
<th>Baseline</th>
<th>Day 14</th>
<th>Relative change (%)</th>
<th>Relative change</th>
<th>p-values for between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4 (10-23 pmol/L)</td>
<td>15.0 (12.5; 15.0)</td>
<td>14.0 (13.5; 15.0)</td>
<td>0.0 (-6.7; 8.0)</td>
<td>14.5 (14.0; 16.0)</td>
<td>40.0 (37.5; 47.5)</td>
<td>185.7 (142.5; 215.5)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aPTT (25.0-38.0 sec)</td>
<td>32.40 (30.30; 36.95)</td>
<td>33.25 (31.85; 36.90)</td>
<td>0.6 (-1.8; 5.5)</td>
<td>32.70 (31.70; 38.60)</td>
<td>31.65 (29.80; 35.65)</td>
<td>-3.4 (-8.4; -1.3)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (51-149%)</td>
<td>80.54 (69.95; 91.13)</td>
<td>74.49 (69.85; 80.03)</td>
<td>-11.1 (-15.6; 3.4)</td>
<td>79.87 (69.30; 87.89)</td>
<td>91.54 (78.53; 108.54)</td>
<td>17.2 (9.6; 20.4)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>VWF:Ag (50-150%)</td>
<td>77.5 (63.0; 98.5)</td>
<td>78.0 (65.5; 92.5)</td>
<td>2.2 (-17.4; 19.7)</td>
<td>77.0 (71.0; 92.5)</td>
<td>102.5 (85.0; 121.5)</td>
<td>25.7 (13.8; 32.9)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>VWF:RiCo (58-172%)</td>
<td>82.5 (57.5; 116.5)</td>
<td>78.5 (61.0; 102.5)</td>
<td>-1.1 (-22.7; 18.4)</td>
<td>91.5 (74.0; 102.5)</td>
<td>112.5 (98.0; 131.0)</td>
<td>23.9 (11.6; 40.1)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Factor VIII (63-173%)</td>
<td>101.0 (84.0; 110.5)</td>
<td>102.6 (84.5; 108.5)</td>
<td>0.6 (-17.7; 9.6)</td>
<td>102.0 (95.0; 105.0)</td>
<td>123.5 (106.0; 135.5)</td>
<td>19.2 (10.0; 27.1)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Factor IX (80-145%)</td>
<td>95.5 (83.0; 101.0)</td>
<td>90.0 (79.0; 100.0)</td>
<td>0.0 (-7.8; 1.7)</td>
<td>91.5 (83.5; 103.5)</td>
<td>105.0 (101.0; 107.0)</td>
<td>14.0 (5.2; 18.2)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Factor X (66-125%)</td>
<td>73.0 (68.5; 80.5)</td>
<td>68.0 (65.0; 82.5)</td>
<td>-7.0 (-11.4; 1.1)</td>
<td>76.5 (67.0; 89.0)</td>
<td>80.5 (69.0; 90.5)</td>
<td>7.0 (-0.5; 12.0)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrinolysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAI-1 (&lt;100 ng/mL)</td>
<td>27.5 (20.5; 36.5)</td>
<td>37.7 (28.0; 58.0)</td>
<td>29.5 (6.2; 68.6)</td>
<td>25.0 (17.5; 45.5)</td>
<td>63.5 (34.0; 100.5)</td>
<td>116.0 (76.6; 227.0)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Clot-lysis time (40-85 min)</td>
<td>49.9 (46.0; 52.5)</td>
<td>50.2 (46.2; 53.4)</td>
<td>1.0 (-3.7; 3.2)</td>
<td>51.9 (46.7; 56.4)</td>
<td>57.0 (53.7; 64.5)</td>
<td>14.3 (9.0; 17.4)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
Bleeding during VKA

FACTORS study:
- 110 persons with bleeding, 220 controls.
- FT4 and TSH measurement
- Low FT4 in normal range: increased bleeding risk
  - <14   3 fold
  - <13   5 fold
- Wide confidence intervals

Debeij et al ISTH 2011
Von Willebrand Factor and Hypothyroidism

Systematic review
- No high quality studies, esp. case reports

- Mucocutaneous bleeding

- VWF Ag median 28 U/dL (range: 4-45)
- VWF Act median 28.5 U/dL (range: <3-55)

- End of this year…

Squizzato et al Haemophilia 2008
Summary thyroid and VTE risk

- Hypothyroidism: Lower VTE risk
- Normal: Balanced VTE risk
- Hyperthyroidism: Higher VTE risk
Cortisol
Known effects cortisol

- Weight
- Fat distribution
- Blood pressure
- Bone
- Metabolism
- Muscle
- Central nervous system
- Skin
Hypercortisolism: endogenous 2009

- Systematic review
- 441 identified publications > 15 studies included
- No high quality studies
- Higher concentrations of factor VIII, factor IX, and von Willebrand Factor, also increase in thrombin generation
- VTE risk 1.9 and 2.5% without surgery
- Postoperative VTE 0 to 5.6% (outlier 20%)

Van Zaane JCEM 2009
Cushing: retrospective study

- All Academic Medical Centers in the Netherlands

- Strict protocol and definitions of
  - Diagnosis
  - Duration of follow-up
    - before diagnosis
    - after diagnosis
    - after surgery
  - Thrombosis and pulmonary embolism

- eCRF

Reminiscence Study
Between 1990 and 2010:

- 473 patients (mean age 42 yrs, 363 women)
- 360 ACTH-dependent pituitary CS.
- 2526 person-years
- 37 patients VTE during the study period

Stuijver JCEM 2011
REMINISCENCE

- Incidence rate of 14.6 [95%CI 10.3-20.1] per 1000 person-years.

- Incidence rate for first-ever VTE prior to treatment was 12.9 (95% CI 7.5-12.6) per 1000 person-years (17 events).

- Postoperative VTE 3.4% (95% CI 2.0-5.9) for ACTH-dependent CS (12 events in 350 patients), despite LMWH

- Most postoperative VTE after stopping LMWH

Stuijver JCEM 2011
Hypercortisolism: exogenous

Hypercoagulability / Venous thrombosis

Inflammation

Corticosteroids
Hypercortisolism: questions

- Anticoagulant therapy?
- Long term use of higher doses of corticosteroids?
- Only temporary risk?
- Role ACTH?
Prolactin
Prolactin

- Higher concentration
  - pregnancy
  - estrogens
  - antipsychotic drugs

- Not only receptors in breast tissue

- Effects on endothelial cells and platelets
Case control study

- Venous thrombosis n=187, controls n=374
- Samples drawn at diagnosis (or suspicion of thrombosis)
- Prolactin > 75th percentile (8 µg/L):
  odds ratio 1.7 (95% CI 1.0 - 2.7)
- Prolactin > p97.5 (16 µg/L):
  odds ratio 4.7 (95% CI 1.8 - 11.8)
- Risk most evident in premenopausal women

Van Zaane ea ATVB 2010
MEGA en prolactin

- Work in progress

- First results indicate higher risk highest percentile
Conclusions (1)

- Several hormones have an influence on the concentration of coagulation factors
- FT4 is associated with VTE risk, even within the normal range
- Overt hyperthyroidism is associated with VTE risk
- Hypothyroidism can cause acquired von Willebrand’s disease
Conclusions (2)

- Endogenous hypercortisolism is associated with a strong increased VTE risk
  - Before and after surgery
  - After surgery: most events after discharge

- Exogenous hypercortisolism: underlying (inflammatory) disease or corticosteroid?

- Hyperprolactinemia may lead to an increased VTE risk as well
Clinical implications?

- Is thrombosis or pulmonary embolism provoked by hyperthyroidism?
  - Risk of recurrence
  - Duration anticoagulant therapy

- Hyperthyroidism in combination with other established thrombosis risk factors: prophylaxis?

- Hypothyroidism: realize effects on VWF in case of emergency (surgery, trauma, bleeding)
Clinical implications?

- Mrs Verdi, 41 years

- 2011 Cushing, ACTH producing pituitary adenoma, diagnosis in another hospital

- Neurosurgeon calls you: Dosis and duration LMWH?
Acknowledgements:

Varese (University of Insubria)
- Alessandro Squizzato, Walter Ageno

Leiden (LUMC)
- Suzanne Cannegieter, Olaf Dekker, Jan Debeij, Frits Rosendaal

Amsterdam (Slotervaartziekenhuis and AMC)
- Bregje van Zaane, Danka Stuijver, Harry Buller, Dees Brandjes, Ton van Zanten, Huib Bout, Jan van Veen, Yvonne van der Heide, Menno Palfenier