DETERMINANTS AND CLINICAL CORRELATES OF INTERINDIVIDUAL VARIATION IN THYROID HORMONE LEVELS

Presentation Thyroid Club Award

Greet Roef

Saturday 25th April 2015
Outline

- General introduction
  - Thyroid hormones
  - Determinants
- Aim
- Study cohorts
- Results
- General conclusion
Thyroid hormones: Synthesis and regulation (1)

**Hypothalamus**

- PVN

**Pituitary**

- TRH down
- TSH down

**Thyroid**

- T4/T3 high
- T4/T3 production down

"T4/T3 high" and "T4/T3 production down" suggest a regulatory feedback mechanism where high levels of T4/T3 stimulate the hypothalamus to decrease production of TRH, which further decreases the release of TSH from the pituitary, ultimately reducing T4/T3 production.
Thyroid hormones: Synthesis and regulation (2)

Hypothalamus

PVN

+ TRH ↑

Pituitary

TSH ↑

Thyroid

T4/T3 production ↑

Hypothalamus

T4/T3 low

T4/T3 production ↑
Thyroid hormones: Metabolism

T4 → D2 → T3 → D3 → T2 → D1 → rT3

ORD → IRD

D3 (D1)
Thyroid hormones: Transport

- Binding proteins:
  - Thyroxine Binding Globulin (TBG)
  - Transthyretin
  - Albumin

- Thyroid hormone transporters:
  - MCT8
  - MCT10
  - OATP1C1
Thyroid hormones: Nuclear binding

- **Cytoplasm**: T3, T4
- **Nucleus**: CoR, RXR, TR, CoA, TRE
- **Gene expression**: ↑ or ↓
Interindividually variation in thyroid hormone levels in healthy subjects

Andersen S et al. JCEM 2002;87:1068-1072
Genetic and non-genetic determinants of thyroid hormone levels
Outline

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HYPERTHYROIDISM  

HYPOTHYROIDISM  

SC HYPERTHYROIDISM  

SC HYPOTHYROIDISM  

NORMAL TSH RANGE  

VARIATION IN FREE HORMONES  

DETERMINANTS  
Genetic  
Environmental/Lifestyle  

CLINICAL EFFECTS  
Bone  
Body composition  
Cardiovascular status
Aims

Genetic variation

Heritability

Lifestyle

VARIATION IN FREE HORMONES

TSH

0  0.1  0.4  1  4  10

NORMAL TSH RANGE

Bone

Body composition

Metabolic parameters

Cardiovascular risk factors

Heart rate, function and structure
Study Cohorts

**SIBLOS**
- 941 men
- 25-45 yrs
- Brothers
- Healthy
- Euthyroid
- Region of Ghent
- DXA, pQCT

**ASKLEPIOS**
- 2500 men and women
- 35-55 yrs
- Not related
- Healthy
- Euthyroid
- Region of Erpe-Mere, Nieuwerkerken
- Echo cor and cardiovascular parameters

**Determinants**
- Bone/body composition/metabolic parameters

**Determinants**
- Cardiovascular and metabolic parameters
Outline

- General introduction
  - Thyroid hormones
  - Clinical effects
  - Determinants
- Aim
- Study cohorts
- Results
- General conclusion
Determinants

Roef G et al, Thyroid, 2013.
Genetic determinants (1)

- Heritability:
  - TSH: 49%
  - FT4: 89%, TT4: 80%
  - FT3: 60%, TT3: 58%
  - TBG: 82%, rT3: 88%
Genetic determinants: SNPs in thyroid hormone pathway

Genetic determinants:
- SNPs in thyroid hormone pathway

Key components:
- PVN
- TRH
- TSH
- T4/T3
- Hypothalamus
- Pituitary
- Thyroid
- TRH
- TRHR
- TSHR
- PDE3B
- OATP1C1
- MCT8
- MCT10
- TRB
- Cell
- DIO1
- DIO2
- Nucleus
Genetic determinants (2): SNPs

- PDE8B: rs4704397~ + TSH, -FT3 and FT4
- TSHR: rs10149689 and rs12050077~ - FT4
- DIO1: rs11206244 and rs2235544 ~ FT3/FT4 and reverse T3
- THR: rs13063628 ~ - TSH
- MCT8: rs5937843 ~ - FT4 and rs6647476 ~ - FT3

Maximal $R^2$ 1.5%

- TRHR: rs7832552; TSHR: rs1991517; DIO2: rs225014; MCT10: rs14399; OATP1C1: rs10444412, rs10770704: no association with thyroid hormone levels
### Age and lifestyle-related determinants

<table>
<thead>
<tr>
<th>Determinant</th>
<th>TSH</th>
<th>FT4</th>
<th>FT3</th>
<th>FT3/FT4</th>
<th>rT3</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.13</td>
<td>-0.18</td>
<td>-0.15</td>
<td>0.06</td>
<td>-0.24</td>
<td>2-3.5%</td>
</tr>
<tr>
<td></td>
<td>p=0.0003</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.07</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.23</td>
<td>0.24</td>
<td>0.36</td>
<td>0.04</td>
<td>0.17</td>
<td>1-3%</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td>p=0.001</td>
<td>p&lt;0.0001</td>
<td>p=0.6</td>
<td>p=0.02</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.04</td>
<td>-0.06</td>
<td>0.15</td>
<td>0.17</td>
<td>-0.09</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>p=0.3</td>
<td>p=0.06</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.009</td>
<td></td>
</tr>
<tr>
<td>Iodine/Creatinine</td>
<td>-0.02</td>
<td>-0.08</td>
<td>-0.04</td>
<td>0.05</td>
<td>-0.1</td>
<td>0.5-2%</td>
</tr>
<tr>
<td></td>
<td>p=0.5</td>
<td>p=0.007</td>
<td>p=0.2</td>
<td>p=0.1</td>
<td>p=0.0007</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.05</td>
<td>0.04</td>
<td>-0.17</td>
<td>-0.16</td>
<td>0.05</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>p=0.1</td>
<td>p=0.3</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.09</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion Determinants

- Heritability is important
- Significant associations with different SNPs in genes from thyroid hormone pathway but effect of each SNP is only limited (max effect of each SNP 1.5% of total variation)
- Age and lifestyle also play a role, maximal effect of each parameter 3.5% of total variation
Clinical Correlates
Variation in thyroid hormone levels and bone parameters

Thyroid parameters:
- TSH
- FT3, FT4
- TT3, TT4
- TBG

Euthyroid range
Siblos cohort

<table>
<thead>
<tr>
<th>Thyroid hormones in relation to areal BMD (DXA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>aBMD lumbar spine (g/cm²)</td>
</tr>
<tr>
<td>aBMD total hip (g/cm²)</td>
</tr>
<tr>
<td>aBMD whole body (g/cm²)</td>
</tr>
</tbody>
</table>
Areal BMD (DXA) according to quartiles of FT₃
Associations between volumetric bone density (pQCT) and thyroid hormones

![Graph showing associations between volumetric bone density (pQCT) and thyroid hormones (TSH, FT3, FT4, TBG). The graph compares cortical bone area and density to trabecular bone area and density across the radius and tibia.](image-url)
Variation in thyroid hormone status even within euthyroid range influences bone mass, density and geometry in men at the age of peak bone mass.

Higher levels of FT3, TT3, TT4 and TBG were negatively related to aBMD and aBMC.

Findings with pQCT, although less consistent, also revealed associations with less favorable bone geometry.
Thyroid hormones & body composition/metabolic parameters

Thyroid parameters:
- TSH
- FT3, FT4
- TT3, TT4
- TBG
- rT3
- Euthyroid range
- Siblos cohort

Body composition/Metabolic parameters
- BMI
- Whole body fat mass
- Whole body lean mass
- Leptin
- Glucose
- Insulin
- HOMA-IR

Roef G et al, Eur J Endocrinol 2012
### Associations between thyroid hormones and body composition

<table>
<thead>
<tr>
<th></th>
<th>TSH (µU/L)</th>
<th>FT3 (pg/dl)</th>
<th>TT3 (ng/dl)</th>
<th>FT4 (ng/dl)</th>
<th>TT4 (µg/dl)</th>
<th>TBG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-0.01 ± 0.03</td>
<td>0.16 ± 0.03</td>
<td>0.14 ± 0.03</td>
<td>-0.02 ± 0.03</td>
<td>0.04 ± 0.03</td>
<td>0.09 ± 0.03</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.01 ± 0.03</td>
<td>0.18 ± 0.03</td>
<td>0.15 ± 0.03</td>
<td>-0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.09 ± 0.03</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>-0.01 ± 0.02</td>
<td>0.04 ± 0.02</td>
<td>0.06 ± 0.02</td>
<td>0.06 ± 0.02</td>
<td>0.10 ± 0.02</td>
<td>0.1 ± 0.02</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>-0.01 ± 0.01</td>
<td>-0.02 ± 0.02</td>
<td>-0.05 ± 0.01</td>
<td>-0.04 ± 0.01</td>
<td>-0.09 ± 0.01</td>
<td>-0.1 ± 0.01</td>
</tr>
</tbody>
</table>
## Associations between thyroid hormones and metabolic parameters

<table>
<thead>
<tr>
<th></th>
<th>TSH (µU/L)</th>
<th>FT3 (pg/dl)</th>
<th>TT3 (ng/dl)</th>
<th>FT4 (ng/dl)</th>
<th>TT4 (µg/dl)</th>
<th>TBG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose (mg/dl)</strong></td>
<td>-0.05 ± 0.03</td>
<td>0.06 ± 0.03</td>
<td>0.06 ± 0.03</td>
<td>-0.02 ± 0.03</td>
<td>0.02 ± 0.03</td>
<td>0.06 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>p=0.1</td>
<td>p=0.09</td>
<td>p=0.08</td>
<td>p=0.6</td>
<td>p=0.6</td>
<td>p=0.06</td>
</tr>
<tr>
<td><strong>Insulin (µU/ml)</strong></td>
<td>0.04 ± 0.03</td>
<td>0.11 ± 0.03</td>
<td>0.12 ± 0.03</td>
<td>-0.02 ± 0.03</td>
<td>0.06 ± 0.03</td>
<td>0.12 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>p=0.1</td>
<td>p=0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.6</td>
<td>p=0.03</td>
<td>p=0.0001</td>
</tr>
<tr>
<td><strong>HOMA IR</strong></td>
<td>0.03 ± 0.03</td>
<td>0.12 ± 0.03</td>
<td>0.12 ± 0.03</td>
<td>-0.02 ± 0.03</td>
<td>0.07 ± 0.03</td>
<td>0.12 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>p=0.3</td>
<td>p=0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.6</td>
<td>p=0.03</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Leptin (µg/L)</strong></td>
<td>0.05 ± 0.02</td>
<td>0.09 ± 0.02</td>
<td>0.08 ± 0.02</td>
<td>0.07 ± 0.02</td>
<td>0.12 ± 0.02</td>
<td>0.11 ± 0.02</td>
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<td>p=0.0002</td>
<td>p=0.003</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>
Thyroid hormones and metabolic profile/cardiovascular risk markers

**Thyroid parameters:**
- TSH
- FT3, FT4, ratio FT3/FT4
- TT3

Euthyroid range

Aasklepios cohort

**Metabolic profile/Cardiovascular risk**
- BMI
- Waist circumference
- Glucose, TG, Cholesterol, blood pressure
- Hs-CRP, IL-6, pulse wave velocity

*Roef G et al, Thyroid, 2013*
Summary Thyroid and Metabolic/Cardiovascular risk

- SIBLOS: higher T3 and TBG:
  - association with less favorable body composition (higher fat mass + leptin levels + lower insulin sensitivity + lower lean mass)

- ASKLEPIOS: higher (F)T3, lower FT4 and higher FT3/FT4 ratio:
  - ↑ risk for metabolic syndrome
  - ↑ CV risk parameters (IL-6, hs-CRP, PWV)
Variation in thyroid hormones and heart rate, cardiac function and left ventricular structure

**Thyroid parameters:**
- TSH
- (F)T3, FT4
- Euthyroid range

**Cardiac parameters:**
- Heart rate
- Echocardiographic parameters:
  - Indices of systolic function
  - Indices of diastolic function
  - LV structure

Roef G et al, THYROID, 2013
Mean heart rate according to quartiles of TT3, FT3 and TSH

Mean heart rate

TT3

FT3

TSH

TSH: 0.3 - 4.2 µU/ml
Summary Thyroid and Heart rate, function and LV structure

- Higher (F)T3 levels within reference range for TSH $\Rightarrow$ ↑ heart rate
- Higher T3 and T4 levels $\Rightarrow$ enhanced atrial contraction and ventricular relaxation
- Higher (F)T3 $\Rightarrow$ trend towards concentric remodelling for LV
Outline

- General introduction
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- General conclusion
General Conclusion

- Heritability
- Genetic variation
- Lifestyle-related determinants

TSH

- 0
- 0.1
- 0.4
- 1
- 4
- 10

NORMAL TSH RANGE

VARIATION IN FREE HORMONES

- Bone
- Body composition
- Metabolic parameters
- Cardiovascular risk factors
- Heart rate, function and structure
Discussion

- TSH-centered definition of thyroid function correct? ⇒ narrowing TSH-range?
- Differential regulation of central and peripheral effects of thyroid hormones
  - Some subjects more sensitive TR alfa than TR beta?
  - Some subjects different distribution of TR alfa?
- Implications for thyroid hormone substitution?
Limitations and perspectives

- Largest part of heritability remains unexplained
- Many determinants still need to be uncovered
- Use of cross-sectional studies $\Rightarrow$ no causal inferences
  - Studies on bone and cardiac parameters: differences in THs $\Rightarrow$ differences in bone and cardiac status
  - Studies on body composition and metabolic risk: less clear $\Rightarrow$ intervention/longitudinal studies
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- Magda Becqué

**Asklepios study**
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- Prof. Dr. Thierry Gillebert
- Marc De Buyzere
- Caroline Van Daele

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- Prof. Dr. Bruno Lapauw
- Dr. Stefan Goemaere
- Dr. Hans Zmierczak
- Dr A-H Batens

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- Stefanie De Buyser
- Joke Van Damme
- Ellen Van Houdenhove
- Annelies Despaey
- Liesbeth Van Huffel
- Dashty Hussein
- Tatjana Sajevets
- Mirra Boer
- Barbara Vandendriessche
- Marijn Carpentier
- Loes Moernaut
VRAGEN-
EXTRA SLIDES
Negative asso’s TBG and bone?

I. Mediated by sex steroids?
   I. No asso TBG and sex steroids
   II. Additional adjustment for sex steroids did not change observed associations
   III. Asso’s with TBG independent from and stronger than those with SHBG
   IV. Negative asso ↔ asso’s with sex steroids and SHBG positive

II. TBG= marker for nutritional status?
   I. A positive association would be expected
   III. Binding proteins potentiate effects of corresponding free hormones?
Influence of body composition on thyroid hormones?

- Body composition
  - Circulating thyroid hormones
    - TBG ~ marker of nutritional status
    - Leptin
      - Central effects
        - TSH
      - Peripheral effects
        - ↑T4 secretion
        - ↑DIO activity
Coefficient of variation

- **INTER-ASSAY CV**: within different runs
  - FT3: max 10%
  - FT4: max 5%
  - TSH: max 5%

- **INTRA-ASSAY CV**: within 1 run (meestal verschillende ‘pools’ vb lage waarde, hoge waarde en gemiddelde waarde:
  - TSH: lage-gemiddeld-hoge pool: tss 1 en 6.7%
  - FT3: lage-midden-hoge pool: tss 2.7 en 3.9%
  - FT4: lage-midden-hoge: tss 2.0 en 5.3%
Phenotype in TRalpha mutations

- **Bone:**
  - Patent cranial sutures
  - Delayed dentition
  - Femoral epiphyseal dysgenesis
  - Wormian bones
  - Growth retardation/Delayed bone age/Adult short stature

- ↓BMR, ↓ heart rate and blood pressure, ↓ colon motility
Urinary iodine excretion: Limitations of single spot UIC

- UIC is coupled to iodine intake
- Iodine intake varies from day to day
- According to some authors: 10 repeat spot urines needed to assess a subject's iodine status
- Single spot UIC: a good determinant of the iodine status of a population
Bone phenotype in DIO2 KO mice

- DIO2 essential for normal osteoblast function
- DIO2 regulates intracellular T3 availability
- DIO2 KO mice:
  - Restricted cellular hypothyroidism in osteoblasts → brittle bones