Malabsorption of thyroxine or non-compliance?

Mieke Bex
department of endocrinology
Case 1: women 58 y – 55 kg

TSH FT₄

Mc Dermott et al. Thyroid 2005;15:386
Apparent resistance to high doses $LT_4$

- Determinants of levothyroxine requirements
- Drugs and conditions interfering with thyroid hormone absorption, transport and metabolism
- Non-compliance: the syndrome of pseudomalabsorption
Determinants of thyroxine requirements

- TSH at diagnosis
- Cause of hypothyroidism
- Body weight
- Age
- FFM
- Replacement vs. suppression

1.6 - 1.8 µg/kg BW
Drugs and conditions interfering with thyroid hormone absorption, transport & metabolism

- Change in circulating thyroxin pool
  - TBG concentration or affinity

- Increase in thyroid hormone metabolism

- Reduced absorption
  - Gastrointestinal disease
  - Substances interfering with absorption
Drugs that interfere with thyroid hormone binding in serum

- Increased serum TBG concentration
  - Estrogens
  - Tamoxifen, raloxifen
  - Heroin
  - Methadone
  - Mitotane
  - Fluorouracil

- Decreased serum TBG concentration
  - Displacement from protein-binding sites

*Surks MI & Sievert R NEJM 1995;333:1688*
Effect of ERT in hypothyroid women

Oral ERT: conjugated estrogens 0.625 mg po + medroxyprogesteron acetate 5 mg 12 days/month
Increased need for thyroxine in hypothyroid women during ERT

Arafah BM NEJM 2001;344:1743

N=18 (7) N=7 (3)

+ 25-50 µg L-T\textsubscript{4}

L-T\textsubscript{4} dose: 104 ± 33 µg
L-T\textsubscript{4} dose: 138 ± 20 µg
Increased need for thyroxine in hypothyroid women during pregnancy

Mandel SJ et al. NEJM 1990;323:91

Alexander et al. NEJM 2004;351:241
Drugs that interfere with thyroid hormone binding in serum

- Increased serum TBG concentration
- Decreased serum TBG concentration
  - Androgens
  - Anabolic steroids (danazol)
  - Slow-release nicotinic acids
  - Glucocorticoids
  - Nephrotic syndrome
- Displacement from protein-binding sites
  - Salicylates (> 2 g/day) & salsalate (1.5-3 g/day)

*Increasing thyroxine requirements in primary hypothyroidism: Don’t forget the urine analysis. Junglee NA et al. J Postgrad Med 2006; 52: 201*
Drugs and conditions interfering with thyroid hormone absorption, transport & metabolism

- Change in circulating thyroxin pool
  - TBG concentration or affinity

- Increase in thyroid hormone metabolism

- Reduced absorption
  - Gastrointestinal disease
  - Substances interfering with absorption
Thyroid hormone metabolism

Pathways of Thyroid Hormone Metabolism

- Glucuronidation (T4G)
- Sulfation (T4S)
- Ether bond cleavage (DIT)
- Oxidative deamination (TA4)
- Deiodination (T3)
- Deiodination (rT3)

Hypothalamus → TRH → Anterior pituitary → TSH → Thyroid gland → T4, T3 → Serum → Liver, Intestine
Drugs affecting thyroid hormone metabolism (increase L-T₄ requirements)

- Inhibition of 5’-monodeiodinase
  - Amiodarone

- Stimulation of the hepatic drug-metabolizing enzyme systems (sulfo- & glucuronosyltransferases)
  - Phenobarbital & rifampicin
  - Phenytoin & carbamazepine
    - + displacement of TH from binding proteins (TBG)
    - 40% decrease in total T₄ (decrease FT₄ = artefact)

- Imatinib

*Figge J & Dluhy RG. Ann Int Med 1990; 113:553*
Resistance to high doses of LT$_4$

- Change in circulating thyroxin pool
  - TBG concentration or affinity

- Increase in thyroid hormone metabolism

- Reduced absorption
  - Gastrointestinal disease
  - Substances interfering with absorption
Absorption of oral thyroxin in man

- Estimation from serum $^{125}$I/$^{131}$I ratio after oral $T_4^{125}$I and iv $T_4^{131}$I administration

- Location
  - Not in stomach
  - Upper jejunum-ileum

- Efficacy
  - Fasting?
  - Morning?

Hays MT J Clin End 1968;749:749
T4 absorption in euthyroid subjects

<table>
<thead>
<tr>
<th>Vehicle T&lt;sub&gt;4&lt;/sub&gt; and content of oral compound</th>
<th>% absorbed mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (euthyroid)</td>
<td></td>
</tr>
<tr>
<td>Tracer + 0.1 mg T&lt;sub&gt;4&lt;/sub&gt; in lactose tablet</td>
<td></td>
</tr>
<tr>
<td>6 fed</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>7 fasting</td>
<td>80 ± 6</td>
</tr>
<tr>
<td>Tracer + 0.1 mg T&lt;sub&gt;4&lt;/sub&gt; in cornstarch tablet</td>
<td></td>
</tr>
<tr>
<td>6 fed</td>
<td>73 ± 11</td>
</tr>
<tr>
<td>6 fasting</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>Tracer + 3.0 mg T&lt;sub&gt;4&lt;/sub&gt; in lactose tablet</td>
<td></td>
</tr>
<tr>
<td>6 fed</td>
<td>48 ± 7</td>
</tr>
<tr>
<td>6 fasting</td>
<td>53 ± 4</td>
</tr>
</tbody>
</table>

Thyroid hormone and the gut. M.T. Hays End Res 1988

Wenzel & Kirschsieper Metab 1977
Effects of evening versus morning thyroxine ingestion in hypothyroid patients

- N=12
- TSH mU/L
  - Morning: 5.1
  - Bedtime: 1.2
  - p < 0.01

- FT4 pmol/L
  - Morning: 19.3
  - Bedtime: 16.7
  - p < 0.01

- TT3 nmol/L
  - Morning: 1.6
  - Bedtime: 1.5
  - p < 0.01

Thyroid hormone absorption

- Mechanism: unknown
- Mean net overall absorption 60-80 %
- Through portal vein to liver
- Liver uptake of $T_4 < T_3$
- First pass effect on biliary secretion
- Inhibition by variety of physical and chemical factors
Thyroxin absorption in health & disease
Case 1: women 58 y – 55 kg

antigliadin 19,2 Au (0-5)
anti tTG 52 U/ml (0-1,9)

Mc Dermott et al. Thyroid 2005;15:386
Coeliac disease and Hashimoto’s thyroiditis

- 104 pt with Hashimoto’s (hypothyroid and Ab +)
  - Coeliac serology (AGA, TGA or EMA)+ 15%
  - Small bowel histology + 5%
- 184 pt with coeliac disease (ESPGHAN criteria)

<table>
<thead>
<tr>
<th>Thyroid Ab</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TPO 19 % - Tg 10 %)</td>
<td>21 %</td>
<td>79 %</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>5 %</td>
<td>76 %</td>
</tr>
<tr>
<td>Subclinical hypo</td>
<td>4 %</td>
<td></td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>12 %</td>
<td></td>
</tr>
</tbody>
</table>

Hadithi, de Boer et al. World J Gastroenterol 2007;13:1715
Reduced absorption

- Short bowel syndromes
  - exception: gastrojejunostomy
- Intestinal disease
  - Celiac disease
  - Giardiasis
- Pancreatic disease
- Liver cirrhosis
- Obstructive liver disease
- Congestive heart failure

Resistance to high doses of LT$_4$

- Change in circulating thyroxin pool
  - TBG concentration or affinity

- Increase in thyroid hormone metabolism

- Reduced absorption
  - Gastrointestinal disease
  - Substances interfering with absorption
Cholestyramine - Colestipol

- Anion-exchange resin
- Impaired absorption oral $T_4$
  - separate ingestion
- Enhancement of fecal $T_4$ excretion
  - $\downarrow$ enterohepatic circulation of $T_4$
  - increase dose

- 50 mg cholestyramine can bind $> 3000 \mu g$ of thyroxine

Solomon BL et al. Clin Endocrinol 1993;38:39

Northcutt et al. JAMA 1969;208:1857
Cholestyramine - Colestipol

- Adjunct for hyperthyroid patients or in levothyroxine intoxication

- Discontinuation only
  3 patients: 258 ± 18 µg

- + cholestyramine 4 x 4 g/d
  58y F 250 µg/day
  64y M 300 µg/day

Sucralfate

- Case reports
- In vitro binding of 63% of $^{125}$I-thyroxine in presence of
  - 175 µg L-T$_4$
  - 875 µg L-T$_4$

Sucralfate: healthy volunteers

**Absorption test**

<table>
<thead>
<tr>
<th>Test Description</th>
<th>% at 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 µg levothyroxin</td>
<td>79.6</td>
</tr>
<tr>
<td>1000 µg levothyroxin 8 h after 2 x 2 g sucralfate</td>
<td>77.7</td>
</tr>
<tr>
<td>1000 µg levothyroxin + 1 g sucralfate 6 h after 4 x 1 g sucralfate</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Sucralfate: patient studies

**Graphs:**
- TSH and TT4 levels over 6 weeks with LT4 and LT4 + 1 g Sucralfate.
- Comparison of baseline, + placebo, and + sucralfate.

**References:**
- Kahn F Ann Intern Med 1993;317
- Campbell JA Ann Intern Med 1994;121:152
Fibre

- Case reports
- In vitro $^{125}\text{I}-\text{T4}$ + wheat bran

![Graph showing adsorbed T4% vs bran (mg/tube)]

![Graph showing TSH levels with and after removal of fibre diet, N=13]

*Liel et al. JCEM 1996;81:857:*
Fibre: healthy volunteers

- 600 µg Levothyroxin
- 600 µg Levothyroxin + 1000 mg polycarbophil
- 600 µg Levothyroxin + 3.4 mg psyllium

N=8

Chiu AC & Sherman SI. Thyroid 1998; 8:667
Ferrous sulfate (300 mg) + T₄

In vitro experiment: formation of ferric-thyroxine complex  
Antacids: aluminium hydroxide

- Case reports
- In vitro: nonspecific adsorption or complexing

\[ \text{LT}_4 \text{ without Al(OH)}_3 \]

2-4 weeks

\[ P = 0.012 \]

\[ N=7 \]

52%

\[ \text{LT}_4 \text{ with Al(OH)}_3 \]

\[ 7.2 \]

Liel YAD Am J Med. 1994 ;97:363

Mersebach H. Pharmacol Toxicol. 1999 ;84:107
Calcium carbonate

- Case reports
- In vitro $^{125}$I-T4 + serial dilutions of CaCO$_3$
  Absorption in acidic environment

Calcium carbonate: patients

Calcium carbonate: volunteers

Singh, N. et al. Thyroid 2001

N=7

1000 µg Levothyroxin + 2 g CaCO₃

1000 µg Levothyroxin

N=7

L-Thyroxine absorption, µg

Time, minutes

T4 alone
T4 + calcium

Singh, N. et al. Thyroid 2001
Other drugs interfering with thyroxine absorption

- **Raloxifene: case reports**
  
  Siray ES Arch Intern Med 2003;163:1367
  
  Garwood CL Pharmacotherapy. 2006;26:881

- **Grapefruit juice: case**

  Lilja JJ Br J Clin Pharmacol 2004;60:337

\[ \text{N= 10 healthy subjects} \]

\[ \text{-11 \%; p < 0.01} \]
Other drugs interfering with thyroxine absorption

- Raloxifene: case reports
  
  Siray ES Arch Intern Med 2003;163:1367
  Garwood CL Pharmacotherapy. 2006;26:881

- Grapefruit juice: case
  
  Lilja JJ Br J Clin Pharmacol 2004;60:337

- Ciprofloxacin: 2 cases

  ![Graph showing thyroid stimulating hormone and free thyroxine levels](image)

  750 mg bid 125 µg L-T₄ → 200 µg

  500 mg bid 150 µg L-T₄
Other drugs interfering with thyroxine absorption

- Raloxifene: case report
  
  Siray ES Arch Intern Med 2003;163:1367

- Grapefruit juice: case report
  
  Lilja JJ Br J Clin Pharmacol 2004;60:337

- Ciprofloxacin: 2 cases
  
  Garwood CL Pharmacotherapy. 2006;26:881

- Simvastatin: 2 cases
  
  Kisch E Ann Int Med 2005;143: 547

- Sevelamer HCl (Renagel): + absorption study

- Chromium picolinate: + absorption study

- Ezetemibe: 1 case; 2 absorption studies —
  
  Ananthakrishnan S et al. Thyroid 2008; 118:493
H$_2$-antagonist & proton pump inhibitors

- Gastric acid suppression in healthy volunteers
  - Pantoprazole 40 mg 1 week: no effect
    
    *Dietrich JW et al Horm Metab Res 2006;38:57*

  - Famotidine (H$_2$-antagonist) 20 mg bid 1 week

  - Esomeprazole 40 mg 1 week
    
    *Ananthakrishnan S et al. Thyroid 2008; 118:493*

![Graphs showing serum gastrin and thyroxine levels before and after drug administration.](figures by EL Mazzaferri (Clinical Thyroidology 14, 2008))
H$_2$-antagonist & proton pump inhibitors

- Gastric acid suppression in healthy volunteers
  - short term studies: no effect
- Effect of PPI in LT$_4$ treated hypothyroid patients

<table>
<thead>
<tr>
<th>Lanzoprazole</th>
<th>TSH (mU/L) after &gt; 2 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=37) +</td>
<td>+ 0.69 ± 1.9</td>
<td>0.035</td>
</tr>
<tr>
<td>(n=55) —</td>
<td>+ 0.11 ± 1.06</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Sachmechi I et al. End Pract 2007; 13:345
Effect of long-term omeprazole and of newly diagnosed H. pylori infection

Centanni M et al. NEJM 2006;354:1787.

Dose L-T4 1.56 1.56 1.70 µg/kg

Dose L-T4 1.58 1.58 2.16 (+37%) µg/kg

omeprazole 40 mg – 6 months for gastroesophagagal reflux
# Thyroxine in Helicobacter infection related gastritis and in atrophic gastritis

Table 2. Daily Thyroxine Requirement in Patients with Multinodular Goiter and *Helicobacter pylori*–Related Gastritis or Atrophic Gastritis, with or without Evidence of *H. pylori* Infection.*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Thyrotropin† mU/liter</th>
<th>Serum Free Thyroxine‡ ng/ml</th>
<th>Median Dose of Thyroxine (interquartile range)§ µg/day</th>
<th>Median Increase in Thyroxine Dose Required µg/kg/day</th>
<th>%</th>
<th>P Value¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference patients</td>
<td>135</td>
<td>0.12±0.05</td>
<td>1.48±0.26</td>
<td>0.1</td>
<td>100 (86–100)</td>
<td>1.53 (1.40–1.62)</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with <em>H. pylori</em>–related nonatrophic gastritis</td>
<td>53</td>
<td>0.11±0.04</td>
<td>1.53±0.22</td>
<td>1.87 (1.78–2.03)</td>
<td>125 (112–125)</td>
<td>22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with atrophic gastritis</td>
<td>60</td>
<td>0.11±0.06</td>
<td>1.50±0.24</td>
<td>1.95 (1.81–2.25)</td>
<td>125 (113–150)</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with concurrent <em>H. pylori</em>–related nonatrophic gastritis</td>
<td>31</td>
<td>0.11±0.04</td>
<td>1.53±0.22</td>
<td>2.05 (1.87–2.34)</td>
<td>150 (125–150)</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients without concurrent <em>H. pylori</em>–related nonatrophic gastritis</td>
<td>29</td>
<td>0.12±0.05</td>
<td>1.49±0.25</td>
<td>1.90 (1.72–2.04)</td>
<td>125 (100–150)</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with increased level of serum thyroid peroxidase antibodies</td>
<td>39</td>
<td>0.11±0.06</td>
<td>1.51±0.19</td>
<td>1.95 (1.81–2.27)</td>
<td>125 (122–150)</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients without increased level of serum thyroid peroxidase antibodies</td>
<td>21</td>
<td>0.11±0.05</td>
<td>1.49±0.26</td>
<td>1.98 (1.82–2.17)</td>
<td>125 (109–156)</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Centanni M et al. NEJM 2006;354:1787.
Thyroxine in Helicobacter infection related gastritis and atrophic gastritis

- Increase in the requirement of oral thyroxine in conditions with impaired gastric acid secretion

- Normal gastric acid secretion major determinant of thyroxine resorption?  
  
  *Centanni M et al. NEJM 2006;354:1787.*

- Gastrointestinal inflammation as common denominator to all conditions (including reflux)?

  *Dietrich JW et al NEJM 2006;354:*
L-thyroxine requirements in patients with parietal cell antibodies (PCA)

Auto-immune thyroiditis

After total thyroidectomy

L-thyroxine requirements in PCA+ patients with auto-immune thyroiditis

Impaired intestinal absorption of L-thyroxine caused by espresso

Benvenga et al. Thyroid 2008; 18:293
Impaired intestinal absorption of L-thyroxine caused by coffee

- Eight case histories
- In vivo & in vitro studies

<table>
<thead>
<tr>
<th>Compound: T&lt;sub&gt;4&lt;/sub&gt; ratio in the mixture</th>
<th>Average % T&lt;sub&gt;4&lt;/sub&gt; recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference = saline</td>
<td>2:1</td>
</tr>
<tr>
<td>Espresso</td>
<td>80</td>
</tr>
<tr>
<td>Al(OH)&lt;sub&gt;3&lt;/sub&gt;+Mg(OH)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>47</td>
</tr>
<tr>
<td>Dietary fibres</td>
<td>45</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>38</td>
</tr>
</tbody>
</table>

Benvenega et al. Thyroid 2008; 18:293 – figures by EL Mazzaferri (Clinical thyroidology 14 2008)
Resistance to high doses of $\text{LT}_4$

- Determinants of levothyroxine requirements
- Drugs and conditions interfering with thyroid hormone absorption, transport and metabolism
- Poor compliance: the syndrome of pseudomalabsorption
Poor adherence to L-T$_4$ replacement

- Elevated TSH despite normal or high FT$_4$

- DD
  - Insufficient L-T$_4$
  - Too early testing after dose increase
    - allow 6-8 weeks
Poor adherence to L-T₄ replacement

- Untreatable hypothyroidism
- Exclude
  - all of the above
- Test pseudomaldigestion
  - Intravenous L-T₄ therapy
  - L-T₄ absorption test
    - Oral dose of 1000 µg

Pseudomalabsorption* treatment

* Ain KB et al. JAMA 1991;266:2118

- Patients with psychopathological features of Munchhausen syndrome or factitious disorder
  - Denial of poor compliance
  - Subtle handling

- Parenteral infusion of L-T<sub>4</sub>
  - 500 µg IV (IM) every 3-4 days

- Supervised oral L-T<sub>4</sub> ingestion
  - e.g. once weekly

Take home message: causes of raised TSH in a patient taking levothyroxine

- Insufficient L-T\(_4\)
- Malabsorption syndromes, e.g. coeliac disease
- Drugs
- Impaired absorption of L-T\(_4\)
- Altered L-T\(_4\) metabolism
- Testing to early after L-T\(_4\) dose increase
- Failure to break down tablets (try crushing)
- Poor adherence to treatment (common)