The Effects of Drugs and Other Conditions Affecting Thyroid Function and Thyroxine Absorption

Michigan AACE Annual Meeting
October 31, 2015

Peter A. Singer, M.D.
Professor of Clinical Medicine
Chief, Clinical Endocrinology
Keck School of Medicine
USC
Disclosures--None

No one wants me
“You’ve got one test, and one pill.”

Jon Singer
Objectives

- Identify which drugs affect thyroid function tests.
- Identify drugs which affect thyroid hormone replacement.
- Identify conditions which affect thyroid replacement.
The Hypothalamic–Pituitary–Thyroid Axis and Sites of Action of Drugs on Thyroid Function

99% of T4/T3 is bound to plasma proteins

Drugs Affecting Thyroid Function—Mechanisms of Action

- Affect TSH secretion
- Produce either hyper or hypothyroidism by directly affecting the thyroid
- Interfere with thyroid hormone transport and metabolism
  - influence TH binding to plasma proteins
  - accelerate metabolism of TH
  - affect T3 production
  - affect GI absorption of TH
Drugs Affecting Thyroid Function—Mechanisms of Action

- Affect TSH secretion
- Produce either hyper or hypothyroidism by directly affecting the thyroid
- Interfere with thyroid hormone transport and metabolism
  - influence TH binding to plasma proteins
  - accelerate metabolism of TH
  - affect T3 production
  - affect GI absorption of TH
Drugs Affecting TSH Secretion

- Glucocorticoids
- Dopamine
- Dobutamine
- Octreotidide
- Bexarotene
Effect of an RXR-selective Ligand on the Pituitary-Thyroid Axis in Humans

27 patients with CTCL treated with bexarotene

p < 0.001

Sherman SI, et al. NEJM, 1999
Serum TSH

TSH (mU/L) vs. hours

- bexarotene
- placebo
Drugs Affecting Thyroid Function—Mechanisms of Action

- Affect TSH secretion
- Produce either hyper or hypothyroidism by directly affecting the thyroid
- Interfere with thyroid hormone transport and metabolism
  - influence TH binding to plasma proteins
  - accelerate metabolism of TH
  - affect T3 production
  - affect GI absorption of TH
Drugs Which Directly Affect the Thyroid

- **Hyperthyroidism**
  - Iodine and iodide containing drugs
    - amiodarone, radiocontrast agents, sski, etc.
  - interferon-alfa, interleukin-2
  - Lithium
  - TKI’s

- **Hypothyroidism**
  - Iodine and iodide containing drugs
  - Lithium
  - Thionamides (MMI, PTU)
  - Thalidomidae
Lithium inhibits TH release

Emerson, et al; JCEM 1973
Amiodarone and Iodine

- Amiodarone dose 200-600mg/day
  - 37% iodine by weight
  - ~10% of molecule deiodinated daily
  - 7-21mg iodide made available daily
- Amiodarone widely distributed in fat and other tissues; released slowly. Effects may persist for months after withdrawal.

Martino et al Endocr Rev 2001;240-54
Effects of Amiodarone on Thyroid

- **Extrinsic effects, due to excess iodine**
  - hypothyroidism, esp in patients with Hashimoto’s
  - thyrotoxicosis, if underlying goiter

- **Intrinsic effects**
  - inhibits 5’ deiodination of T4 (thus, decrease in T3 production, and increase in rT3).
  - Blocks T3 receptor binding to nuclear receptors (thus decrease in tissue effects)—and, hypothyroid-like effects
  - may have direct toxic effect on follicular cells (*thyroiditis*)
Prevalence of Thyrotoxicosis and Hypothyroidism in 229 Patients Chronically Treated with Amiodarone

# Amiodarone-Induced Thyrotoxicosis

<table>
<thead>
<tr>
<th></th>
<th>Iodine Excess (type 1)</th>
<th>Thyroiditis (type 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx thyroid disease</td>
<td>Often</td>
<td>No</td>
</tr>
<tr>
<td>Goiter</td>
<td>Nodular</td>
<td>No</td>
</tr>
<tr>
<td>RAIU</td>
<td>Varies</td>
<td>Low</td>
</tr>
<tr>
<td>IL-6</td>
<td>NI or sl high</td>
<td>High</td>
</tr>
<tr>
<td>Treatment</td>
<td>MMI</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>
Interferon (INFα) Induced Thyroid Abnormalities

- Autoantibodies (40-50%, HCV> HBV)
- Hypothyroidism (2-20%)
- Hyperthyroidism (2-3%)
  - Destructive thyrotoxicosis (60-75%)
  - Graves’ disease (25-40%)

Baseline Ab status | % developed abn TFT
--- | ---
Positive (89) | 46 %
Negative (947) | 5%

Koh, *Thyroid*, 1997
Tyrosine Kinase Inhibitors and Thyroid Function

- First generation (eg, sunitinib, sorafenib) and second generation (eg, nilotinib, disatinib) frequently cause thyroid abnormalities:
  - Hypothyroidism 38-85 %!!
  - Transient hyperthyroidism (thyroiditis) in up to 40 % of patients who develop hypothyroidism.
    - 8/25 patients with RCC/sunitinib developed hypo T, with 6/8 preceded by hyper T. (Grossman et al; Clin Endo (Oxf) 2008:669-672)
  - TPO antibodies not a predictor, and mostly negative
Sunitinib and Hypothyroidism

Makita et al. *Thyroid* 2010
How do TKI’s Cause Thyroid Dysfunction?

- Inhibition of iodine uptake?
- Inhibition of thyroid peroxidase?
- Direct toxic effect on thyrocytes?
- Hypothyroidism a result of preceding transient thyrotoxicosis?
Drugs Affecting Thyroid Function—Mechanisms of Action

- Affect TSH secretion
- Produce either hyper or hypothyroidism by directly affecting the thyroid
- Interfere with thyroid hormone transport and metabolism
  - influence TH binding to plasma proteins
  - accelerate metabolism of TH
  - affect T3 production
  - affect GI absorption of TH
Drugs Altering TFT’s Without Changing FT4 or FT3 Levels

- **Increase TBG**
  - Estrogens
  - Tamoxifen
  - Relaxofine
  - Methadone
  - Heroin
  - 5-fluouracil
  - Clofibrate
  - Mitotane

- **Decrease TBG**
  - Androgens
  - Danazol
  - Glucocorticoids
  - L-asparaginase
  - Niacin (slow release)
## Drugs Affecting Metabolism and Production

<table>
<thead>
<tr>
<th><strong>T4 Metabolism</strong></th>
<th><strong>T3 Production</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rifampin</td>
<td>• Amiodarone</td>
</tr>
<tr>
<td>• Carbamazepine (Tegretol)</td>
<td>• Propylthiouracil</td>
</tr>
<tr>
<td>• Phenytoin (Dilantin)</td>
<td>• Dexamethasone (&gt;4mg/d)</td>
</tr>
<tr>
<td>• Phenobarbitol</td>
<td>• Propranolol (&gt;160 mg/d)</td>
</tr>
<tr>
<td>• Amiodarone</td>
<td>• Metoprolol, atenolol (in hyperthyroidism)</td>
</tr>
<tr>
<td>• Zoloft</td>
<td></td>
</tr>
</tbody>
</table>
L-T4 Absorption and Food Intake

- Approximately 62 – 82% of levothyroxine absorbed after oral administration; occurs within 3 h, mainly in duodenum, jejunum and ilieum.

**AACE/ATA guideline:**
- Standard recommendation: take L-T4 60 min before breakfast
  - Data establishing this are minimal
- Debate regarding better absorption before sleep (no food for 4 h after dinner) vs. 30 min before breakfast

*Garber J et al; Endo Pract, Dec 2012; Thyroid, Dec 2012*
Drugs and Conditions Affecting Absorption

- **Drugs**
  - Calcium carbonate
  - Cholestyramine resin
  - Sucralfate
  - Ferrous sulfate
  - Aluminum hydroxide
  - Colestipol hydrochloride
  - Raloxifene
  - Sevelemer
  - Lanthanum carbonate
  - PPI’s
  - TKI’s?

- **Conditions**
  - Food
  - Fiber
  - Espresso!
  - Celiac disease
  - IBD
  - Jejunoileal bypass
  - *H. Pylori*
  - Chronic gastritis
Iron Ingestion and Levothyroxine Therapy

Ferrous Sulfate Effect on TSH Levels in Patients With Hypothyroidism

Effect of Calcium on L-T4 Absorption

Effect of Calcium on L-T4 Absorption

1000 µg T4 + 500 mg Ca

Effect of Lanthanum or Colesevelam Co-Administration on T4 AUC

![Bar graph showing the effect of Lanthanum or Colesevelam co-administration on T4 AUC.](image)

FIG. 2. Mean ± SE area (above baseline) under the serum T₄ concentration curve in six normal subjects receiving levothyroxine alone or simultaneously with study medications. Co-administration of colesevelam HCl or lanthanum carbonate significantly decreased the absorption area compared to T₄ given alone.

Effects of PPIs on Serum TSH

- PPIs: can decrease LT₄ bioavailability up to 50%²²-²⁵

- PPIs may impair tablet LT₄ absorption by increasing gastric pH; decreasing dissolution⁴,¹³

### Mean changes in TSH

<table>
<thead>
<tr>
<th></th>
<th>TSH (µIU/ml)</th>
<th>Mean Changes in TSH (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline TSH</td>
<td>1.95 (±1.1)</td>
<td></td>
</tr>
<tr>
<td>Follow Up TSH</td>
<td>1.84 (±1.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline TSH</td>
<td>2.34 (±1.3)</td>
<td></td>
</tr>
<tr>
<td>Post PPI TSH</td>
<td>3.0 (±2.0)</td>
<td></td>
</tr>
</tbody>
</table>

*P = 0.035*

TSH changes in the control group and study group.

10 pts w/ MNG before and during 40 mg omeprazole/d
Watch out, Starbucks!

FIG. 1. Incremental rise of serum thyroxine (T4) after ingestion of two 0.1 mg levothyroxine (L-T4) tablet that were swallowed with half glass of water (filled squares connected by discontinuous lines) or a cup of espresso (empty triangles connected by continuous lines) in the indicated patients or volunteers. These patients and volunteers were available to allow comparison of the effect of coffee on T4 intestinal absorption with the effect of bran (empty circles connected by continuous lines). Note how volunteer no. 5 deviates from the other two volunteers and two patients, because coffee increased, not decreased, T4 absorption.

Benvenega et al, Thyroid 2008
Medical Conditions

- Chronic gastritis
  - Autoimmune
  - *H. Pylori* infection
  - Proton-pump inhibitors
- Celiac disease
- Lactose intolerance
- Jejunoileal bypass or other bowel resection
- Inflammatory bowel disease
- Intestinal parasites
GUIDELINES FOR THE TREATMENT OF HYPOTHYROIDISM

Table 5. Medications Reducing Levothyroxine Absorption, as Shown in Trials and Case Studies in Hypothyroid Patients

<table>
<thead>
<tr>
<th>Medications</th>
<th>Type of study</th>
<th>No. of subjects</th>
<th>TSH values mIU/L (w/o medication, c/w with medication)</th>
<th>Binding study?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>Prospective, cross-over trial</td>
<td>20</td>
<td>1.6 vs. 2.7</td>
<td>Yes, LT₄ adsorbs to calcium</td>
<td>132</td>
</tr>
<tr>
<td>PPI (lansoprazole)</td>
<td>Retrospective chart review of PPI initiation</td>
<td>55 controls, 37 taking PPI</td>
<td>Increased by 0.11 vs. 0.69</td>
<td>n/a</td>
<td>135</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Case reports</td>
<td>2</td>
<td>Increased while taking cholestyramine</td>
<td>Yes, cholestyramine bound to LT₄</td>
<td>136</td>
</tr>
<tr>
<td>Selevamer</td>
<td>Retrospective chart review</td>
<td>67</td>
<td>Mean TSH 20 with selevamer</td>
<td>n/a</td>
<td>139</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>Nonrandomized, prospective trial</td>
<td>14</td>
<td>TSH 1.6 vs 5.4</td>
<td>Yes, T₄ formed a complex with iron</td>
<td>140</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>Case report (patient also pregnant and post partum)</td>
<td>1</td>
<td>TSH 1.3 c/w 29</td>
<td>n/a</td>
<td>141</td>
</tr>
<tr>
<td>Aluminum-containing antacid</td>
<td>Case report</td>
<td>1</td>
<td>TSH 1.1 vs. 36</td>
<td>n/a</td>
<td>142</td>
</tr>
<tr>
<td>Aluminum-containing antacid</td>
<td>Nonrandomized, prospective study</td>
<td>5</td>
<td>TSH increased from 2.6 to 7.2</td>
<td>Yes, T₄ adsorbed to antacid</td>
<td>143</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Case report</td>
<td>1</td>
<td>TSH increased from normal to 30</td>
<td>n/a</td>
<td>144</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Placebo-controlled, randomized</td>
<td>9</td>
<td>TSH 2.7 vs. 4.6</td>
<td>n/a</td>
<td>145</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Case report</td>
<td>1</td>
<td>TSH normal vs. 9.4</td>
<td>n/a</td>
<td>148</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Case report</td>
<td>1</td>
<td>TSH 0.03 vs. 73</td>
<td>n/a</td>
<td>150</td>
</tr>
<tr>
<td>Cation exchange resin</td>
<td>Case report</td>
<td>1</td>
<td>TSH 0.67 vs. 139</td>
<td>Yes, T₄ adsorbed to sodium polystyrene sulfonate</td>
<td>151</td>
</tr>
</tbody>
</table>

n/a, not applicable; TSH, thyrotropin.
### GI Disorders and LT4 Absorption

<table>
<thead>
<tr>
<th>Disorder</th>
<th>↑ LT4 Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>27%\textsuperscript{16}</td>
<td>Normalizes when treated</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>22% \textsuperscript{16}</td>
<td>Treatment reverses malabsorption in 1/3\textsuperscript{17}</td>
</tr>
<tr>
<td>Both atrophic gastritis/<em>H. pylori</em></td>
<td>34%\textsuperscript{16}</td>
<td>Treatment reverses malabsorption in 1/3\textsuperscript{18}</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>50-100%\textsuperscript{18}</td>
<td>Normalizes with Gluten-free diet</td>
</tr>
<tr>
<td>Bowel resection or bypass</td>
<td>Delayed +/- malabsorption\textsuperscript{19}</td>
<td>Normalizes with higher dose of LT\textsubscript{4}</td>
</tr>
<tr>
<td>Giardiasis/Other parasitic Disease</td>
<td>&gt; 200%\textsuperscript{20}</td>
<td>Normalizes when treated</td>
</tr>
</tbody>
</table>

Northeast Scotland Survey:
17,500 Patients on L-T4 Replacement

- 190 pts taking more than 225 µg in 2009
  - 2.4 µg/kg in men; 2.8 µg/kg in women
- No cause for high dose in 36%
- Gastric parietal cell antibodies in 22%
- Medication interference in 21%
- Compliance problems in 17%
- Celiac disease antibodies in 4%

Chronic Autoimmune Gastritis

- 391 patients receiving T4 Rx for hypothyroidism with TSH at target and no interfering meds or medical conditions
- 155/391 (40%) had parietal cell ab and 236 (60%) did not
- L-T4 requirement significantly higher in PCA+ patients (1.24 ± 0.40 vs. 1.06 ± 0.36 µg/kg/d)

Chronic Autoimmune Gastritis

Autoimmune Gastritis in Hashimoto’s

- 2016 consecutive Hashimoto’s patients screened for parietal cell antibodies
- 29.7% were positive
- Prevalence of +ab increased from 13% in age 10 – 20 y to 42% in age 80+ y

Effect of Vitamin C on Absorption of Levothyroxine In Patients With Hypothyroidism and Gastritis

- 31 pts with gastritis and hypothyroidism difficult to control
- Given T4 with and without 500 mg Vit C in 120 mL water
- With Vit C, TSH decreased on same T4 dose:
  - 11.1 (median) control to 4.2 mU/L
  - TSH normalized in 17/31 (55%)
  - Mean decrease was 69%

Frequency of Celiac in Hashimoto’s

104 patients with Hashimoto’s thyroiditis

Positive coeliac serology
- IgA anti-gliadin (IgA-AGA) 9 (8.6%)
- IgG anti-gliadin (IgG-AGA) 7 (6.7%)
- IgA anti-tissue transglutaminase (TGA) 8 (7.6%)
- IgA anti-endomysium (EMA) 6 (5.7%)

Positive HLA-DQ2 and/or HLA-DQ8 53 (50.9%)

Small bowel histology
(15 of 16 coeliac seropositive patients)
- Normal 9 (8.6%)
- Marsh I 1 (1%)
- Marsh III 5 (4.8%)

Prevalence of Hypothyroidism in Celiac Disease

- Multicenter Italian study: 31/241 (12.9%)

- Univ. Vermont: 22/152 (14.5%)

- Sardinian children 34/324 (10.5%)
58 y/o woman with celiac disease

<table>
<thead>
<tr>
<th>Date of review</th>
<th>TSH level mU/L (n = 0.6–4.3)</th>
<th>FT$_4$ level pmol/L (n = 9–24)</th>
<th>LT4 dose at prescribed (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 8, 1996</td>
<td>&gt; 100</td>
<td>&lt; 5.2</td>
<td>50</td>
</tr>
<tr>
<td>October 22, 1996</td>
<td>61.2</td>
<td>9.1</td>
<td>Increased to 100</td>
</tr>
<tr>
<td>May 2, 1997</td>
<td>24</td>
<td>11.7</td>
<td>100</td>
</tr>
<tr>
<td>November 10, 1997</td>
<td>31.1</td>
<td>9.9</td>
<td>Increased to 125</td>
</tr>
<tr>
<td>April 30, 1998</td>
<td>Not tested</td>
<td>15.2</td>
<td>125</td>
</tr>
<tr>
<td>April 30, 1999</td>
<td>Not tested</td>
<td>18.4</td>
<td>125</td>
</tr>
<tr>
<td>November 18, 1999</td>
<td>16.44</td>
<td>11</td>
<td>Increased to 150</td>
</tr>
<tr>
<td>May 3, 2000</td>
<td>4.84</td>
<td>10.1</td>
<td>Increased to 175</td>
</tr>
<tr>
<td>November 1, 2001</td>
<td>1.6</td>
<td>15</td>
<td>175</td>
</tr>
<tr>
<td>November 5, 2002</td>
<td>11.18</td>
<td>11</td>
<td>Increased to 200</td>
</tr>
<tr>
<td>February 4, 2003</td>
<td>0.72</td>
<td>14.5</td>
<td>200</td>
</tr>
<tr>
<td>April 16, 2003</td>
<td>0.05</td>
<td>21.2</td>
<td>Reduced to 150</td>
</tr>
<tr>
<td>July 23, 2003</td>
<td>0.2</td>
<td>14.1</td>
<td>Reduced to 125</td>
</tr>
</tbody>
</table>

Gluten-free diet commenced

### Percent Hypolactasia (Lactose Intolerance) by Race, Ethnicity, Country of Origin

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southeast Asians</td>
<td>98%</td>
</tr>
<tr>
<td>Asian Americans</td>
<td>90%</td>
</tr>
<tr>
<td>Alaskan Eskimo</td>
<td>80%</td>
</tr>
<tr>
<td>African-American Adults</td>
<td>79%</td>
</tr>
<tr>
<td>Mexicans (rural communities)</td>
<td>74%</td>
</tr>
<tr>
<td>North American Jews</td>
<td>69%</td>
</tr>
<tr>
<td>Greek Cypriots</td>
<td>66%</td>
</tr>
<tr>
<td>Cretans</td>
<td>56%</td>
</tr>
<tr>
<td>Mexican American Males</td>
<td>55%</td>
</tr>
<tr>
<td>Indian Adults</td>
<td>50%</td>
</tr>
<tr>
<td>African American Children</td>
<td>45%</td>
</tr>
<tr>
<td>Indian Children</td>
<td>20%</td>
</tr>
<tr>
<td>Descendents of N. Europeans</td>
<td>5%</td>
</tr>
</tbody>
</table>

From Nutritional Genomics Center, UC Davis; Assembled by R. Rodriguez from various sources.
Decrease in TSH Levels After Lactose Restriction in Hashimoto's Thyroiditis Patients With Lactose Intolerance

- 83 HT patients taking LT4 were enrolled in study, and LI diagnosed in 76% of the HT patients
- 38 patients with LI started on a lactose-restricted diet for 8 weeks while continuing same dose of LT4; their TSH significantly decreased, while TSH in 12 patients without LI did not change during the 8 weeks
- Conclusions: LI occurs at a high frequency in HT patients; lactose restriction leads to decreased levels of TSH
- LI should be considered in hypothyroid patients who require increasing LT4 doses, have irregular TSH levels, and are resistant to LT4 treatment

Roux-en-Y Gastric Bypass Surgery: T4 Malabsorption

**Table 1** Thyroid parameters measured at the indicated times in four patients who underwent bariatric surgery between 2009 and 2011. Patients were receiving oral L-T4 in either tablet or liquid form as indicated.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before surgery L-T4 in tablet form</th>
<th>12 Months after surgery L-T4 in tablet form</th>
<th>14 Months after surgery L-T4 in liquid form</th>
<th>17 Months after surgery L-T4 in tablet form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-T4 (µg)</td>
<td>TSH</td>
<td>fT4</td>
<td>fT3</td>
</tr>
<tr>
<td>1</td>
<td>200</td>
<td>4.2</td>
<td>12.7</td>
<td>3.1</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>3.1</td>
<td>12.9</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>3.9</td>
<td>11.7</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>3.6</td>
<td>10.9</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*L-T4* levothyroxine, *TSH* thyrotropin, *fT4* free tyroxine, *fT3* free triiodothyronin

Intestinal Parasites: Giardiasis

Rafaela Rde F, et al\(^1\):

- Increased levothyroxine requirement in a woman with previously well-controlled hypothyroidism and intestinal giardiasis

Thank you!

Questions?