Hyperthyroidism

and Hypothyroidism

Gilbert H. Daniels M.D.
Objectives

- To understand the differential diagnosis of hyperthyroidism
- To understand the growing role of drug-induced thyroid dysfunction
- To appreciate the significance of subclinical hyperthyroidism
- To understand what causes a change in L – T4 dosing.
- To understand the T4/T3 controversy for hypothyroidism
Hyperthyroidism
TSH Assays

1st generation 1965-1985
2nd generation 1984-
3rd generation 1989-
4th generation 1992-

TSH uU/ml

10
1
0.1
0.01
0.001

Hyperthyroidism - High or Normal RaI U

- Hot Nodule
- Toxic Nodular Goiter
- Graves Disease
- TSH Induced Hyperthyroidism
- HCG Induced Hyperthyroidism
Hyperthyroidism - High or Normal RaI U

- Hot Nodule
- Toxic Nodular Goiter
- Graves Disease
- TSH Induced Hyperthyroidism
- HCG Induced Hyperthyroidism
HCG vs. TSH

Yoshikawa et al
JCEM 1989; 69: 891

HCG vs. TSH
Pregnancy: TSH

9562 women - excluding hypothyroidism

Hot Nodule

TSH

T 4

T 3
Hot Nodule
Hypothyroid: 5% in our experience
Toxic Nodular Goiter

- TSH
- T4
- T3
Toxic Nodular Goiter
Iodine Induced Hyperthyroidism

KI 5gtts/d
2 mos

T 4 Upper limits of normal

Free T 4 Upper limits of normal

Vagenakis et al
NEJM 1972;287:523
Graves’ Disease

$^{123}$I Uptake 78 %
Graves’ Ophthalmopathy
Thyroid Dermopathy: Pretibial Myxedema

Cheng CP et al NEJM 2005; 352: 918
Elecsys TRab

<table>
<thead>
<tr>
<th>GD Zone</th>
<th>Graves’ Disease</th>
<th>Painless Thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 IU/L</td>
<td>n = 382 (99.7%)</td>
<td>n = 1 (0.3%)</td>
</tr>
<tr>
<td>1.5 IU/L</td>
<td>n = 25 (69.4%)</td>
<td>n = 11 (30.6%)</td>
</tr>
<tr>
<td>0.8 IU/L</td>
<td>n = 7 (26.9%)</td>
<td>n = 19 (73.1%)</td>
</tr>
<tr>
<td>PT Zone</td>
<td>n = 0 (0%)</td>
<td>n = 218 (100%)</td>
</tr>
</tbody>
</table>

Kamijo et al. Endocr Journal 2010; 57: 895
Graves’ Hyperthyroidism Therapy

- Block Synthesis
  Methimazole or PTU

- Ablate or Remove the Thyroid
  Radioiodine or Surgery
Anti-Thyroid Drugs

Minor Toxicity (5%)

- Fever
- Rash
- Joint Pains
Anti-Thyroid Drugs

Major Toxicity

• Agranulocytosis (0.2 - 0.5 %)

• Toxic Hepatitis (PTU)

• Cholestatic Jaundice (MMI)

• Vasculitis (ANCA positive) (PTU)
Propylthiouracil: 100 mg q 8 h

Methimazole: 30 mg q d

Nicholas et al. S. Med J 1995; 88: 973
\textbf{Iodine Therapy - Graves’ Disease}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{graph.png}
\caption{Percent Hypothyroid vs. Years after Ra I}
\end{figure}

Holm L-E et al, J Nuc Med 1982; 23:103
Alemtuzumab: Reconstitution Autoimmunity

Anti-CD52 Antibody for MS

Thyroid dysfunction in 73/220 pts

Daniels et al.  
J Clin Endocrinol Metab 2014; 99:80-9

Percent patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>34%</td>
</tr>
<tr>
<td>Graves</td>
<td>22.2%</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>6.9%</td>
</tr>
<tr>
<td>SAT</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
Hyperthyroidism Therapy

TSH Suppression

Weeks

Free T4 ng / dl

TSH mU / L

< 0.05

0.10

1.0

10.0

100.0

0

0.5

1.0

5.3

4.0

3.7

1.3

0
Recent Patient

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt; 0.01 mU/L</td>
<td>0.5 – 5.0</td>
</tr>
<tr>
<td>FT4</td>
<td>2.8 ng/dl</td>
<td>0.8 – 1.8</td>
</tr>
<tr>
<td>TT3</td>
<td>597 ng/dl</td>
<td>70 – 180</td>
</tr>
<tr>
<td>TBI (TRAb)</td>
<td>35</td>
<td>(&lt; 1.4)</td>
</tr>
</tbody>
</table>

There was nothing wrong with this patient!!

The patient is on Biotin for hair loss!!
<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt; 0.01mU/L</td>
<td>&lt; 0.01mU/L</td>
<td>0.4-5 mU/L</td>
</tr>
<tr>
<td>T4</td>
<td>10.7 ug/dl</td>
<td>25.0 ug/dl</td>
<td>4-11 ug/dl</td>
</tr>
<tr>
<td>FT4</td>
<td>1.7 ng/dl</td>
<td>3.5 ng/dl</td>
<td>0.8-1.8 ng/dl</td>
</tr>
<tr>
<td>TT3</td>
<td>179 ng/dl</td>
<td>530 ng/dl</td>
<td>80-180 ng/dl</td>
</tr>
</tbody>
</table>
Subclinical Hyperthyroidism

- Low serum TSH
- Normal free T4
- Normal T3 or free T3
Subclinical Hyperthyroidism

- Patient may or may not be symptomatic!
- Exclude other causes of decreased serum TSH.
FT4 vs. TSH

Spencer et al
JCEM 1990; 70: 453
Subclinical Hyperthyroidism

- Uncertain effects on overall mortality.
- Some studies show increased cardiovascular mortality, greater with TSH < 0.1 mU/L compared to 0.1 – 0.4
- Endogenous subclinical hyperthyroidism is associated with osteoporosis and possibly fractures in post-menopausal women, particularly with TSH < 0.1.

Ross DS  Thyroid 2016: 26: 1343
Atrial Fibrillation: Ten Year Prevalence

Age > 60

P = 0.005

Sawin et al NEJM 1994; 331: 1249

Percent

30
20
10
0

TSH ≤ 0.1

28 %

TSH > 0.4 - 5.0

11 %
• Treat TSH < 0.1 if ≥ 65 years of age; with cardiac risk factors, heart disease or osteoporosis; in post-menopausal women not on estrogens or bisphosphonates; or if hyperthyroid symptoms.

• Consider treating persistent TSH < 0.1 in asymptomatic individuals < 65 even without risk factors or symptoms.

Ross DS  Thyroid 2016: 26: 1343
Subclinical Hyperthyroidism 2016 Guidelines

- Consider treating TSH below lower limits of normal but $\geq 0.1$ if $\geq 65$ years of age, with cardiac risk factors, heart disease or osteoporosis; in post-menopausal women not on estrogens or bisphosphonates; and if hyperthyroid symptoms.

- TSH below lower limits of normal but $\geq 0.1$ in asymptomatic patients under age 65 may be observed if no cardiac disease or osteoporosis.

Ross DS  Thyroid 2016: 26: 1343
Subclinical Hyperthyroidism

- There are no large scale randomized, placebo controlled intervention trials.
Hyperthyroidism - 0 or near nil RaI U

- Factitious hyperthyroidism
- Painful subacute thyroiditis
- Painless subacute thyroiditis
- Amiodarone destructive thyroiditis
- Excess iodine
- Struma ovarii
- Metastatic follicular carcinoma
Destructive Thyroiditis

T3 and T4

TSH

Ral uptake = 0
Destructive Thyroiditis: Subacute Thyroiditis

- Hyperthyroid
- Hypothyroid
- Recovery

**Graph:**
- **T4 (ug/dl):**
  - 0
  - 3
  - 6
  - 9
  - 12

- **TSH (uU/ml):**
  - 0
  - 3.5

**Months:**
- 0
- 3
- 6
- 9
- 12

**Legend:**
- **T4**
- **TSH**
Destructive Thyroiditis

$^{123}$ I Scan

4cm

SSN

24 hr Ral uptake 0.04 %
<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Country</th>
<th>FU</th>
<th>Number</th>
<th>Preg Screen</th>
<th>PPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino</td>
<td>1982</td>
<td>Japan</td>
<td>6</td>
<td>507</td>
<td>N</td>
<td>5.5 %</td>
</tr>
<tr>
<td>Jansson</td>
<td>1984</td>
<td>Sweden</td>
<td>5</td>
<td>460</td>
<td>N</td>
<td>6.5 %</td>
</tr>
<tr>
<td>Freeman</td>
<td>1986</td>
<td>USA</td>
<td>3</td>
<td>212</td>
<td>N</td>
<td>1.9 %</td>
</tr>
<tr>
<td>Nikolai</td>
<td>1987</td>
<td>USA</td>
<td>3</td>
<td>238</td>
<td>N</td>
<td>6.7 %</td>
</tr>
<tr>
<td>Lervang</td>
<td>1987</td>
<td>Denmark</td>
<td>12</td>
<td>591</td>
<td>N</td>
<td>3.9 %</td>
</tr>
<tr>
<td>Fung</td>
<td>1988</td>
<td>UK</td>
<td>12</td>
<td>901</td>
<td>Y</td>
<td>16.7 %</td>
</tr>
<tr>
<td>Rasmussen</td>
<td>1990</td>
<td>Denmark</td>
<td>12</td>
<td>736</td>
<td>N</td>
<td>3.3 %</td>
</tr>
<tr>
<td>Rajatanavin</td>
<td>1990</td>
<td>Thailand</td>
<td>12</td>
<td>812</td>
<td>N</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Roti</td>
<td>1991</td>
<td>Italy</td>
<td>12</td>
<td>372</td>
<td>N</td>
<td>4.8 %</td>
</tr>
<tr>
<td>Walfish</td>
<td>1992</td>
<td>Canada</td>
<td>12</td>
<td>1376</td>
<td>N</td>
<td>6.0 %</td>
</tr>
<tr>
<td>Stagnaro-Green</td>
<td>1992</td>
<td>USA</td>
<td>6</td>
<td>545</td>
<td>Y</td>
<td>8.8 %</td>
</tr>
</tbody>
</table>
Post-Partum Thyroiditis: Antibodies

Stagnaro-Green A. Thyroid
Today 16: 1 : 1993

Prospective Studies
Post-Partum Thyroiditis: Clinical

- Hypothyroidism
  - Alone: 36%
  - Then Hyperthyroidism: 26%
- Hyperthyroidism
  - Alone: 38%

Stagnaro-Green
Thyroid Today
16; 1 : 1993
Post-Partum Thyroiditis - Hypothyroidism

Lucas A et al
Thyroid 2005; 15: 1177

- Hyperthyroidism alone: n = 16
- Hyper then hypo: n = 10
- Hypothyroidism alone: n = 19
Factitious hyperthyroidism

Painful subacute thyroiditis

Painless subacute thyroiditis

Amiodarone destructive thyroiditis

Excess iodine

Struma ovarii

Metastatic follicular carcinoma
## Amiodarone Induced Hyperthyroidism

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (10%)</th>
<th>Type 2 (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MNG</strong></td>
<td>Nodules</td>
<td>No nodules</td>
</tr>
<tr>
<td><strong>Graves</strong></td>
<td>No nodules</td>
<td>Nodules</td>
</tr>
<tr>
<td><strong>SAT</strong></td>
<td>No nodules</td>
<td>No nodules</td>
</tr>
<tr>
<td><strong>TRAb</strong></td>
<td>Neg</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Ra I U</strong></td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>Flow</strong></td>
<td>NI or hi</td>
<td>NI or hi</td>
</tr>
<tr>
<td><strong>Response to prednisone</strong></td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

- **Amiodarone Induced Hyperthyroidism**
- **Type 1 (10%)**
- **Type 2 (90%)**
Amiodarone Induced Thyrotoxicosis Type 2

Mean Free T3 (ng/dL)

- Prednisone 30 mg daily

Amiodarone Stopped

Time (Days)

Bogazzi et al
JCEM 2003; 88:1999
Primary Hypothyroidism

TSH

T4

T3

X
Atrophic Primary Hypothyroidism

- Radioactive Iodine
- Surgery
- External Radiation
- Drugs
- Atrophic thyroiditis
- TSH Receptor Antibodies
- Mutant TSH receptor
- Congenital Hypothyroidism
External Radiation: Hypothyroidism

Boomsma MJ et al
Int J Rad Oncol Bio Phys
2012; 84: e 351

Hypothyroidism %

Mean Thyroid Dose (Gy)

Brachytherapy: Hypothyroidism

Thyroid Volume 10 cc
Thyroid volume 15 cc
Thyroid volume 20 cc
Thyroid volume 25 cc
Tyrosine kinase inhibitor licensed for therapy of renal cell carcinoma and GIST tumors.
Sunitinib Hypothyroidism

Desai et al.
Ann Int Med 2006
145:660

TSH U/L vs Weeks

Sunitinib
Levothyroxine

Weeks
10 20 30 40 50 60 70 80 90 100

0 50 100 150 200 250 300

1.6 1.3 3.9 4.3 2.5 6.2 8.8 1.0 2.3 2.8 0.6

288 52 23 18
Sunitinib: Abnormal Thyroid Tests

- Abnormal TSH 26/42 (62%)
- High TSH 15/42 (36%)
- Low TSH 4/42 (10%)
- Transient high TSH 7/42 (16%)
- Life table analysis suggests may be 100%
Goitrous Primary Hypothyroidism

- Hashimoto’s Thyroiditis
- Painful Subacute Thyroiditis
- Silent Subacute Thyroiditis
- Drugs
- Transient Post Ral
- Biosynthetic Defects
- Iodine Deficiency
- Consumptive
- Congenital (Ectopic)
Intrathoracic Fibrous Tumor

Type 3 Deiodinase

Aw et al. JCEM 2014: 99: 3965
Goitrous Primary Hypothyroidism

- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis
- Hashimoto’s Thyroiditis

Dr. Hakaru Hashimoto
Archiv fur Klinische Chirurgie
1912; 97: 219
Hashimoto’s Thyroiditis
Premature Gray Hair

Hall et al. Color Atlas of Endocrinology 1979
Vitiligo

Lancet 2002; 360: 1639
NEJM 2004; 26: 2698
Anti-TPO Antibodies

Mariotti et al
JCEM 1990; 71:661

Control
Graves’
Hashimoto’s
Is it worthwhile diagnosing Hashimoto’s thyroiditis in euthyroid individuals?
Miscarriages

- TPO Ab - (n = 869): 2.4%
- TPO Ab + (n = 58): 13.8%
- TPO Ab + L-T4 (n = 57): 3.5%

P < 0.01
P < 0.05
Thyroid Antibodies

Stagnaro-Green A.
Thyroid Today 16: 1 : 1993

Antibody Positive

Antibody Negative

Percent

Percent

Miscarriage

PPT

Miscarriage and PPT

Miscarriage

PPT
Thyroid Failure

Serum TSH

Serum fT4

Serum T3

Normal
Subclinical Hypothyroid
Moderate Hypothyroid
Severe Hypothyroid
Serum TSH U/L vs. Free T4 nmol/L

- x 2
- x 90

> x 90

Spencer et al, JCEM 1990; 70: 453

Undetectable
Subclinical Hypothyroidism

- Normal T4
- Normal Free T4
- Elevated TSH
Subclinical Hypothyroidism

- Exclude other causes of elevated TSH
- Patient may be symptomatic or asymptomatic!!
Disease free: no thyroid disease, goiter, thyroid meds: 16.533

Total population: 17,353

Hollowell et al
JCEM 2002; 87:489
Subclinical Hypothyroidism

Antibody Prevalence

NHANES III

Hollowell et al
JCEM 2002; 87: 489

Percent TPOAb + TgAb

TSH mU/L

4.0 - 4.5
4.5-5.0
5.0 - 10
10 - 20
> 20

28.0
30.9
54.6
85.2
96.5
Subclinical Hypothyroidism: Follow-Up

- **TSH Normalized**: 52.1%
- **Overt Hypothyroidism**: 85.7%

Mean 31.7 months
n = 104
Mean Age: 62.2

- 5-9.9: 5.6%
- 10-14.9: 13.3%
- 15-19.9: 4.8%

Diez JJ. JCEM 89: 4890, 2004
**Subclinical Hypothyroidism**

- With TSH 4.7 - 10 mU/L: most are asymptomatic.
- No good evidence for L-T4 symptomatic benefit in this range.
- No good evidence for L-T4 cholesterol lowering in this range.
- There may be symptomatic and cholesterol benefit with TSH > 10.

Persistent TSH 4.6 – 19.99 mIU/L (mean 6.4 ± 2.01 mIU/L)
• Mean age 74.4 years

• Randomized placebo controlled trial. Goal of therapy to normalize TSH.

• Major endpoints Hypothyroid Symptom score or Tiredness score.

• Of note at baseline 27% had 0 hypothyroid symptoms and 8.7% had 0 tiredness score.
Subclinical Hypothyroidism Elderly

Levothyroxine (n=332)

- Hypothyroid Score 12 months: 16.6 ± 16.9
- Tiredness Score 12 months: 16.7 ± 17.5

Placebo (n = 337)

- Hypothyroid Score 12 months: 28.7 ± 20.2
- Tiredness Score 12 months: 28.6 ± 19.5

P = 0.99
P = 0.77

Stott et al. NEJM 2017 epub
Rodondi N et al. Subclinical Hypothyroidism and the risk of coronary heart disease and mortality.

JAMA 2010: 304: 1365
Rodondi et al.

- TSH 0.5 - < 4.5: Euthyroid
- TSH > 4.5 - < 20: Subclinical hypothyroid
- Re-analyzed 11 prior prospective cohorts
- Subclinical hypothyroid: n = 3450
- Euthyroid: n = 51,837
Subclinical Hypothyroidism Overall

- No difference in CHD events: HR 1.18 (CI 0.99-1.42)
- No difference in CHD mortality: HR 1.14 (CI 0.99-1.32)
- No difference in overall mortality: HR 1.09 (CI 0.96 - 1.24)
Subclinical Hypothyroidism by TSH

TSH 4.5 - 6.9 mU/L

- No difference in CHD events: HR 1.00 (CI 0.86-1.18)
- No difference in CHD mortality: HR 1.09 (CI 0.91-1.3)
- No difference in overall mortality: HR 1.06 (CI 0.96 - 1.17)

TSH 7.0 - 9.9 mU/L

- No difference in CHD events: HR 1.17 (CI 0.96-1.43)
- Increased CHD mortality: HR 1.42 (CI 1.03-1.95)
- No difference in overall mortality: HR 1.02 (CI 0.84 - 1.24)

Rodondi N et al. JAMA 2010: 304: 1365
Subclinical Hypothyroidism by TSH

TSH 10 - 19.9 mU/L

- Increase in CHD events: HR 1.89 (CI 1.28-2.8)
- Increase in CHD mortality: HR 1.58 (CI 1.1-2.27)
- No difference in overall mortality: HR 1.22 (CI 0.8 - 1.87)

Rodondi N et al. JAMA 2010: 304: 1365
Fatal and non-fatal ischemic heart disease events

Subclinical Hypothyroidism: ages 40 – 70 (n = 3093)
TSH 5 – 10 mU/L

Cumulative Events
Multivariate analysis
Not a randomized trial

No Levothyroxine Rx
Levothyroxine Rx

Razvi S et al.
Arch Int Med 2012; 172: 811

Follow-up months
Subclinical Hypothyroidism: Cardiovascular Risk

- Ultimately requires an adequately powered randomized placebo-controlled therapeutic trial!
- These are particularly difficult to carry out given the normalization of TSH in almost 50%.
What to do when TSH elevated

Patient on thyroid hormone:

generally increase dose.
What to do when TSH elevated

Patient not on thyroid hormone:

Repeat measurement.

Use common sense!
My TSH is 6. I feel terrible. Nothing is right. I’m cold, tired, hungry, constipated and depressed. Please treat me with thyroid hormone!

Subclinical Hypothyroidism
My TSH is 6. I feel fine! Do I really have to be treated with thyroid hormone for the rest of my life?
To treat or not to treat ?
# Subclinical Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Treat ?</th>
<th>Observe ?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>TSH mU/L</td>
<td>&gt; 10</td>
<td>5 - 10</td>
</tr>
<tr>
<td>+ Thyroid Ab</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Post-Ral</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Goiter</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Why not screen for and treat all subclinical hypothyroidism?

- Consequences of subclinical hyperthyroidism. Up to 20% on T4 have low TSH.
- Consequences of labeling.
- Patients taking levothyroxine don’t feel as well as controls (Saravanan).
- Consequences of multi-drug therapy in elderly.
- Cost of drug, tests and visits, if unnecessary.
Gussekloo et al. Thyroid status, disability and cognitive function and survival in old age. *JAMA* 2004; 292: 2591-2599
Cumulative Mortality in the Aged

Gussekloo et al
JAMA 2004; 292: 2591

Cox regression P = .03 for trend
Elevated serum TSH

- Age 20-29 97.5 centile for TSH: 3.45 mU/L
- Age 80 + 97.5 centile for TSH: 7.5 mU/L
- Older patients: 70% with TSH > 4.5 mU/L are within their age-specific reference range.

Surks and Hollowell JCEM 2007: 92: 4575
Levothyroxine

- 7 day half life
- Single daily dose
- Absorption: 80%
Levothyroxine Therapy

Weeks

TSH uU/ml

T 3 ng/dl

T 4 ug/dl

Levothyroxine Therapy

0.1 mg

0.2 mg /day

T 3

T 4

TSH

Levothyroxine Therapy

0.1 mg

0.2 mg /day

T 3

T 4

TSH

Levothyroxine Therapy

0.1 mg

0.2 mg /day

T 3

T 4

TSH

Levothyroxine Therapy

0.1 mg

0.2 mg /day

T 3

T 4

TSH

Levothyroxine Therapy

0.1 mg

0.2 mg /day

T 3

T 4

TSH
Generic Levothyroxine

• To date there have **not** been consistent problems with generics although there are anecdotal reports of problems.

• We are currently treating most of our patients with generic L-T4

• Non-insurance cost of generic levothyroxine 0.125 mg 90 pills ranges from $12 - $92.
Thyroid Hormone Adjustment

- Worsening hypothyroidism
- Increased clearance
- Decreased absorption
- Pregnancy
- Age
- Poor compliance
Increased Clearance

- Phenytoin
- Carbamazepine
- Rifampin
- Phenobarbital
- Imatinib
- Other Tyrosine Kinase Inhibitors
Thyroid Hormone Adjustment

- Worsening hypothyroidism
- Increased clearance
- Decreased absorption
- Pregnancy
- Age
- Poor compliance
Decreased Absorption

- Iron
- Aluminum hydroxide
- Calcium
- Lanthanum
- Cholestyramine and other resins
- Sucralfate
- Raloxifene
- Ciprofloxacin
- GI disorders - cryptic sprue
- Decreased stomach acid
- Food - including espresso
- “Insoluble Pills”
Increased Levothyroxine Requirement

- Estrogen
- ? Sertraline
Before pregnancy

During pregnancy

Serum TSH U/L

Thyroid Hormone Therapy

Mandel et al NEJM 1990; 323: 91
High L-T4 Requirement in a Community Setting

T4 dose > 225 mcg

N = 125

Interfering meds: 20.8%
Compliance: 16.8%
Parietal Ab: 21.6%
Celiac: 4.7%
No cause: 36.1%

Robertson HMA et al
Thyroid 2014; 24: 1765
Once upon a time there was a symptomatic hypothyroid patient with an elevated serum TSH. Thyroid hormone therapy was begun. The TSH normalized, the symptoms disappeared and the patient lived happily ever after!

Fable

88 – 90 % feel well on levothyroxine therapy.
Saravan et al. Clin Endocrinol 2002; 57: 577

Levothyroxine Therapy

Thyroid Symptom Questionnaire

Percent TSQ > 3

46.8
35.0
48.6
35.0

p=<0.001
p<0.001

462 patients
535 controls

Patients
Controls
“NI”TSH

Saravan et al. Clin Endocrinol 2002; 57: 577
Possible Explanations

- Failure to titrate TSH to “low normal”
- T3 supplementation required
- Co-morbid disorders including depression
- Having an illness ("Labeling")
- Coincidence ("squeaky wheel gets tested")
- Hashimoto’s thyroiditis
Levothyroxine Dose Titration

No Difference

- Weight
- Zulewski score
- Visual Analog Scale
- SF-36 Questionnaire
- GHQ-28
- Thyroid Symptom Q
- Treatment Satisfaction

Walsh et al. JCEM 2006; 91:2624-30
Possible Explanations

- Failure to titrate TSH to “low normal”
- T3 supplementation required
- Co-morbid disorders including depression
- Having an illness (“Labeling”)
- Coincidence (“squeaky wheel gets tested”)
Super Hormone
<table>
<thead>
<tr>
<th>Improvement in metrics</th>
<th>No improvement in metrics</th>
<th>Prefer T4/T3</th>
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</thead>
<tbody>
<tr>
<td><strong>Bunevicius</strong></td>
<td>Escobar</td>
<td>Bunevicius</td>
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<tr>
<td></td>
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<td>Escobar</td>
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<tr>
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<td></td>
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<td>Apelhof</td>
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<tr>
<td></td>
<td>Rodriguez</td>
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</tr>
</tbody>
</table>

* some categories worse
General Health Questionnaire

Deiodinase Genotype

Panicker et al JCEM
2009; 94: 1623

P = 0.03

T4 + T3
T4

T T

T C

C C

TA

Visit

Visit

Visit

GHQ Score

15
13
11
9

1 2 3

1 2 3

1 2 3

Visit

Visit

Visit
Panicker et al. (JCEM, 2009; 94: 1623).
T4 + T3 Conclusions

- There may be some patients who (are genetically pre-disposed to) feel better on the combination therapy. Whether this is due to a physiological role of T3 or a pharmacological property of T3 in some individuals is uncertain.

- There is a strong placebo effect.

- Even if we agree that T3 is necessary, we do not know the ideal way to prescribe T3.
What I do when patients don’t feel well on T4

- Realize that many patients don’t feel well (with or without T4)

- Look for other concomitant disorders: these include iron deficiency and anemia in pre-menopausal women, sleep disturbances including sleep apnea, and depression.

- Titrate TSH to lower normal range (despite the controlled trials).

- Consider adding T3 (liothyronine) 5 mcg in the a.m. and 5 mcg in early afternoon. Initially I don’t adjust the levothyroxine (unless TSH very low at the time) but ask patients to call in two months. If feeling better I check TFTs and continue the medication. If no difference I stop the medication.
What might the future hold for thyroid hormone analogues?

How would you like a thyroid hormone analogue which causes weight loss, corrects lipid abnormalities, does not stimulate appetite or the heart, does not weaken bones or muscle and reverses vascular plaque and fatty liver?

The future may be here.....
T3 covalently linked to Glucagon causes T3 action in liver and fat without raising systemic T3 or stimulating heart and bone.
T3-Glucagon effects

- Hepatic T3 counteracts diabetogenic effect of glucagon
- Corrects dyslipidemia, obesity and hyperglycemia in diet-induced-obesity mouse model.
- Improves non-alcoholic steatosis and atherosclerosis in preclinical disease models in mice
- No cardiac toxicity.
- No increased circulating T3.
- Increased uncoupling protein in fat cells promotes energy expenditure.
Summary Points

- Hyperthyroidism is not just Graves’ disease
- Many drugs cause thyroid dysfunction (e.g. amiodarone, alemtuzumab, sunitinib and others).
- Hypothyroidism is primarily Hashimoto’s thyroiditis but think of other etiologies.
- For inappropriate TSH elevation in patients on thyroid hormone, consider increased metabolism, decreased absorption, pregnancy or poor compliance.
- Possible but limited role for T3 supplementation.
Hyperthyroidism

and Hypothyroidism