Where do we stand with T3, Bioidenticals, and Branded Products

Lou Haenel
Sweetgrass Endocrinology
Roper St Francis

Topics For Discussion
Thyroid Physiology
Evaluation of Thyroid Dosing
Subclinical Disease/ Pregnancy
Alternate Hormone Replacement Option
Use of T3 Therapy
Thyroid Hormone Synthesis

Normal Gland Production includes 80% T4 and 20% T3
Additional Production of T3 comes from Peripheral deiodination in liver, muscle, kidney
T4 has Lower Binding Affinity For Thyroid Receptor Than T3
T4 May Also Be Converted to Reverse T3

T4 to T3 conversion


Narrow Therapeutic Range Drugs

“...those containing certain drug substances that are subject to therapeutic drug concentration monitoring and/or where product labeling indicates a narrow therapeutic range designation” 1,2

- Unless otherwise indicated by a specific guidance, traditional limit of 80-125% is recommended
- Levothyroxine sodium is a compound with a narrow therapeutic range
- Other common NTI drugs: Warfarin, digoxin, phenytoin

Defining Ranges for Serum TSH

**Lab reference range**
- Defined by values in “normal” population
- 0.4-5.5 mIU/L

**Individual’s range**
- Much narrower than reference range
- ±0.5 mIU/L over time

**Target range**
- Goals for thyroxine treatment of specific conditions
- Hypothyroidism: 0.5-2.5 mIU/L
- Thyroid cancer: undetectable to 0.5 mIU/L

---


---

Individual TSH Normal Range

- 16 caucasian men
- 24-52 yrs (median 36)
- 16 no Hx thyroid disease, goiter, or medication
- Blood samples:
  - Monthly (0900-1200)
  - Stored frozen
  - Analyzed random order in same assay run

**Participants**
Mean +/- 2 SD = 1.27 (0.16 - 2.39)


---

Each subject’s TSH range was unique
Width of individual range ≈1/2 of group

- Widest range (#1)
- Narrowest range (#12)

TSH Change Following 12.5 mcg Change in Levothyroxine Dose

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17</td>
<td>0.89</td>
<td>1.32</td>
<td>3.10</td>
</tr>
</tbody>
</table>

Median TSH Change (mIU/L)

Same LT, Product Different Doses

TSH Change Following 25 mcg Change in Levothyroxine Dose (n=722)

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.27</td>
<td>1.12</td>
<td>2.10</td>
<td>4.58</td>
</tr>
</tbody>
</table>

Median TSH Change (mIU/L)

Same LT, Product Different Doses

Mild Hypothyroidism & Mild Thyrotoxicosis Definitions

TSH

FT₄

Overt Mild Euthyroidism Mild Overt

Hypothyroidism Thyrotoxicosis
Unusual Situations

Subclinical Hyperthyroidism
Subclinical Hypothyroidism
Pregnancy

Subclinical Thyroid Dysfunction
Screening

If TSH is high and FT₄ is not recorded then:
• Repeat test with FT₄
• Wait a minimum of 2 weeks and a maximum of 12 weeks
• Test high risk individuals (eg, pregnant, Hx of disease, > 60 yrs)
• Patient preferences are important in deciding management
Further research and more definitive data are needed


Subclinical Thyroid Disease: Conclusions

• Data supporting associations of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment are few
• Consequences of subclinical thyroid disease (serum TSH 0.1-1.45 mIU/L or 4.5-10.0 mIU/L) are minimal
  • Panel recommended against routine treatment
• Insufficient evidence to support population-based screening
  • However, aggressive case finding is appropriate in
    • Pregnant women
    • Women older than 60 years
    • Others at high risk for thyroid dysfunction

Natural History for the Progression of Subclinical Hypothyroidism

- Over 10-year follow-up: (n=82 women)
  - 34% progressed to overt hypothyroidism
  - 57% remained subclinically hypothyroid
  - 9% euthyroid
- Greatest predictors of overt disease
  - Initial TSH level
  - Presence of anti-thyroid antibodies


Subclinical Hypothyroidism
Progression to Overt Disease

- 258 healthy elderly followed x 4 yrs
  - 13.2% had subclinical hypothyroidism based on normal T₄ and elevated TSH
- 4 yrs later:
  - 33% overtly hypothyroid
  - 80% of those with (+) Ab's


Should We Be Using T3?
Combined T₄/T₃ Therapy
Summary of Studies

<table>
<thead>
<tr>
<th>Benesvicor NEJM</th>
<th>Benesvicor JN</th>
<th>Watch JCEM</th>
<th>Santa JCEM</th>
<th>Clyde JAMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Thyroiditis</td>
<td>33</td>
<td>11</td>
<td>110</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>46%</td>
<td>100%</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>Duration T₄ Dose</td>
<td>5 wks</td>
<td>5 wks</td>
<td>10 wks</td>
<td>15 wks</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>12.5</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>TSH T₄/T₃ vs T₄</td>
<td>0.5 vs 0.8</td>
<td>0.7 vs 0.8</td>
<td>1.8 vs 1.7</td>
<td>2.0 vs 2.1</td>
</tr>
<tr>
<td>Cognitive Mood</td>
<td>Improved</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Improved</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>SHBG Cholesterol</td>
<td>Higher</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
<td>Higher</td>
</tr>
</tbody>
</table>


Hypothyroidism

T₄/T₃ Combination Therapy

- N=23 (20F, 3M) 23-69 yo
- 21 After-sx/radioiodine; 2 autoimmune thyroiditis
- Two 12-week periods
- No washout
- Run-in 4 weeks with T₄
- 1st period: 100-175 mcg T₄
- 2nd period: 5% of T₄ substituted with T₃

In replacement therapy using LT₄ plus T₃ compared with LT₄ monotherapy
- Cognitive performance and mood do not improve
- Combination therapy is not superior to monotherapy

Combination therapy is not superior to monotherapy

Serum TSH and FT₃ and FT₄ in:
- 9 hypothyroid with hx autoimmune
- 14 hypothyroid (non-autoimmune)

TSH more suppressed in combination therapy

Cognitive performance and mood do not improve with combination therapy

<table>
<thead>
<tr>
<th>Mood scores</th>
<th>T₃</th>
<th>T₄/T₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory</td>
<td>6.1±6.9</td>
<td>3.7±3.8</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory</td>
<td>32.7±6.3</td>
<td>32.0±6.6</td>
</tr>
<tr>
<td>Memory (Digit Symbol Test)</td>
<td>55.4±11.6</td>
<td>55.5±10.3</td>
</tr>
<tr>
<td>Working (Digit Span Test)</td>
<td>11.9±2.1</td>
<td>12.3±1</td>
</tr>
</tbody>
</table>

While not statistically significant, this small study shows that cognitive performance and mood do not improve with combination therapy
Hypothyroidism

**T₄/T₃ Combination Therapy**

- N=28 subjects with overt hypothyroidism
- Randomized double-blind crossover
- Patients euthyroid on 100 mcg LT₄
- 3 8-week periods
  - Maintained on 100 mcg
  - Switched to 75 mcg LT₄ and 5 mcg T₃
  - 14:1 proportion of endogenous production
  - 87.5 mcg LT₄ with 7.5 mcg add-on T₃


**Combination tx resulted in:**
- ↑ FT₄
- Slightly increased TSH in standard combination
- Slightly ↓ TSH in the add-on T₃ combination
- Unchanged FT₃
- No difference in primary or secondary outcomes


<table>
<thead>
<tr>
<th></th>
<th>Euthyroid</th>
<th>Combination Therapy</th>
<th>Add-on Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>1.95±1.44</td>
<td>2.56±1.65</td>
<td>1.09±1.33</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.7±5.4</td>
<td>6.6±5.3</td>
<td>7.3±5.0</td>
</tr>
<tr>
<td>Depression</td>
<td>12.4±5.3</td>
<td>13.2±4.9</td>
<td>13.1±5.3</td>
</tr>
<tr>
<td>Digital Span</td>
<td>12.4±5.3</td>
<td>13.2±4.9</td>
<td>13.1±5.3</td>
</tr>
<tr>
<td>QOL (SF-36)</td>
<td>60.9±17.1</td>
<td>62.2±17.5</td>
<td>61.8±17.3</td>
</tr>
</tbody>
</table>

Oppenheimer, Braverman, Ladenson….

“In Practice Most Serious Problems Arise from Flawed Human Behaviors NOT Improper Drug Formulation”
Desiccated Natural Thyroid

- Desiccated thyroid is a drug prepared from dried porcine (pig) thyroid.
- Desiccated thyroid was the only thyroid drug available in the early 1900s, until levothyroxine was introduced in the 1950s.
- Natural thyroid fell out of favor as the synthetic product was touted as more modern and stable.
- Since the 1980s, desiccated thyroid has enjoyed a resurgence, primarily with older doctors and holistically-oriented physicians who claim that it resolves symptoms better than synthetics in some patients.
- Several brands of desiccated thyroid are available by prescription, including Nature-Throid and Armour Thyroid.
Why not conduct BE studies in subjects with no thyroid function (i.e. athyreotic)?

- Precedent in estrogen products
- Multi-dose, steady-state cross-over
- Validate with known difference (e.g., 100 vs. 88 mcg)

Bioequivalence criteria should be tied to clinically relevant marker

- TSH is the medically acceptable marker
- Must define maximally acceptable change in TSH level changes for patients’ safety

Rx controversies:

“As of 2012 there are no controlled trials supporting the preferred use of desiccated thyroid hormone over synthetic L-thyroxine in the treatment of hypothyroidism or any other thyroid disease.”

- American Thyroid Association

Could Switching Products Pose a Patient Risk?

Why not conduct BE studies in subjects with no thyroid function (i.e. athyreotic)?

- Precedent in estrogen products
- Multi-dose, steady-state cross-over
- Validate with known difference (e.g., 100 vs. 88 mcg)

Bioequivalence criteria should be tied to clinically relevant marker

- TSH is the medically acceptable marker
- Must define maximally acceptable change in TSH level changes for patients’ safety