Thyroid update

- T3 replacement in hypothyroidism
- Subclinical thyroid disease
- Differentiated thyroid cancer

Clinical case

51 year old woman with Graves’ disease treated with $^{131}$I in 2003

Not felt well since Rx. Weight gain 30 pounds; unable to lose weight despite being on a diet and exercising regularly

On L-thyroxine 0.088 mg daily - FT4 18 (9 to 24); TSH 0.71 (0.4 to 4.0)

Requests more L-thyroxine or T3 therapy

Normal T4 and T3 production
**T3 levels in athyreotic patients after T4 supplementation**


- 33 patients
  - 5 wk T4 + T3
  - 5 wk T4
  - 5 wk T4


- 50 µg T4 substituted with 12.5 µg T3

---

**Table: Cognitive performance**

<table>
<thead>
<tr>
<th>Test or Scale</th>
<th>After Thyroidect (N=33)</th>
<th>After Thyroidect (N=33)</th>
<th>P Value</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Symbol Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pairs recalled correctly</td>
<td>5.5±2.3</td>
<td>6.3±2.1</td>
<td>0.04</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Time (sec)</td>
<td>58±15</td>
<td>56±16</td>
<td>0.07</td>
<td>—</td>
</tr>
<tr>
<td>Raw score</td>
<td>48±12</td>
<td>47±12</td>
<td>0.76</td>
<td>&gt;43</td>
</tr>
<tr>
<td>Digit Span Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Backward recall of digits</td>
<td>5.3±1.6</td>
<td>6.0±1.3</td>
<td>0.06</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Forward recall of digits</td>
<td>6.9±3.9</td>
<td>6.9±1.8</td>
<td>0.99</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Visual Scanning Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (sec)</td>
<td>73±23</td>
<td>71±25</td>
<td>0.15</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Total correct</td>
<td>58±2</td>
<td>59±2</td>
<td>0.53</td>
<td>&lt;56</td>
</tr>
<tr>
<td>Errors</td>
<td>1.7±1.8</td>
<td>1.5±2.1</td>
<td>0.58</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Mood scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>9.8±7.7</td>
<td>7.9±5.3</td>
<td>0.10</td>
<td>&lt;11</td>
</tr>
<tr>
<td>Spielberger State-Trait Anxiety Inventory</td>
<td>44±11</td>
<td>48±8</td>
<td>0.38</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Profile of Mood States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>33±28</td>
<td>24±24</td>
<td>0.01</td>
<td>—</td>
</tr>
<tr>
<td>Fatigue-inertia</td>
<td>9.3±4.3</td>
<td>7.2±3.9</td>
<td>0.001</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Depression-depression</td>
<td>13±9.9</td>
<td>10.5±8.9</td>
<td>0.01</td>
<td>&lt;26</td>
</tr>
<tr>
<td>Anger-hostility</td>
<td>9.1±7.3</td>
<td>7.3±5.2</td>
<td>0.04</td>
<td>&lt;17</td>
</tr>
<tr>
<td>Confusion-bewilderment</td>
<td>5.3±4.5</td>
<td>4.3±3.5</td>
<td>0.13</td>
<td>&lt;17</td>
</tr>
<tr>
<td>Tension-anxiety</td>
<td>8.5±5.3</td>
<td>7.7±5.4</td>
<td>0.23</td>
<td>&lt;21</td>
</tr>
<tr>
<td>Vigor-activity</td>
<td>12±4.6</td>
<td>13±3.7</td>
<td>0.39</td>
<td>&gt;9</td>
</tr>
</tbody>
</table>

**Walsh et al. JCEM 88: 8543 (2003)**

- RCT, crossover design (n = 110)
- Usual T4 vs T4 + T3 with 50ug T4 replaced with 10ug T3
- TSH higher when on T3

**Sawka et al. JCEM 88: 4551 (2003)**

- RCT, parallel design (n=39)
- Patients with depressive symptoms
- No change in QOL, mood, hypothyroid symptoms

**Clyde et al. JAMA 2952 (2003)**

- RCT, parallel design (n=44)
- T4 vs T4 + T3 with 50ug T4 replaced with 7.5ug T3 BID
- No change in QOL, neuropsychological tests


- RCT, crossover design (n=23)
- T4 vs T4 + T3 16.1 molar ratio
- No change in well being or cognitive function

**5 wk T4 + T3**

- 16 thyroiditis
- 17 thyroid CA

**5 wk T4**

- 5 wk T4

---

![Graph showing T3 levels in athyreotic patients after T4 supplementation](image-url)
Conclusion

- There is currently no evidence that T4 + T3 combination is more effective than T4 therapy alone in the treatment of hypothyroidism

Thyroid preparations

<table>
<thead>
<tr>
<th></th>
<th>Peak at 2 to 4 hours; half life 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>Peak at 2 to 4 hours; half life 1 day</td>
</tr>
<tr>
<td>T3</td>
<td>1 grain = 60 mg; 38 µg T4 &amp; 9 µg T3 ~ equivalent to 75 to 88 µg T4</td>
</tr>
<tr>
<td>Dessicated porcine thyroid (Armor)</td>
<td>1 grain = 60 mg; 38 µg T4 &amp; 9 µg T3 ~ equivalent to 75 to 88 µg T4</td>
</tr>
<tr>
<td>Liotrix (Thyrolar)</td>
<td>1 grain 50 µg T4 and 12.5 µg T3</td>
</tr>
</tbody>
</table>

Clinical case

52 year old woman with type 1 diabetes for 50 yrs Also has Hashimoto’s thyroiditis and is on Lthyroxine 75 µg daily with TSH levels between 1.7 and 3.0

Started on Cytomel (T3) 5 µg daily at request of her psychiatrist for treatment of depression in 2007. Her depression has stabilized and improved

Augmentation strategy with T3

<table>
<thead>
<tr>
<th>Goodwin et al Am J Psych 139: 34 (1982)</th>
<th>Failed imipramine or amitriptyline for 4 weeks (n=12)</th>
<th>25 to 50 ug T3 added</th>
<th>Beneficial effect</th>
<th>Depressive and bipolar disorder included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gitlin et al J Affect Disord 13: 267 (1987)</td>
<td>Unresponsive to imipramine for 4 wks; (n = 16)</td>
<td>25 ug T3 or placebo for 2 wks each Double blind placebo controlled; crossover</td>
<td>No beneficial attributed to T3</td>
<td>Concern about crossover design and washout period</td>
</tr>
<tr>
<td>Joffe et al Arch Gen Psych 50:387 (1993)</td>
<td>Unresponsive to imipramine or desipramine (n=50)</td>
<td>37.5 ug T3 or 900 mg lithium or placebo for 2 wks Double blind</td>
<td>10/17 responded to T3 9/17 responded to lithium 3/16 responded to placebo</td>
<td>Short duration</td>
</tr>
</tbody>
</table>
Depressed patients on tricyclic alone followed by treatment with T3 (n=12)

**Conclusion**

Small studies suggest a beneficial effect of T3 as augmentation therapy for therapy resistant depression. Larger studies are required.

**Clinical case**

50 year old man complaining of fatigue

TSH 4.9 (0.4 - 4.0); FT4 14 (9 – 24)

Tg ab 65 (<20); TPO ab 1.51 (positive > 1.19)

US showed heterogeneous gland consistent with thyroiditis
Log linear relationship between TSH and T4 – a 2 fold change in T4 causes a 100-fold change in TSH

Whickham population survey (n=2779)
Prevalence of TSH ≥ 6.0 with normal T4 levels

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28/1000</td>
<td>75 /1000</td>
</tr>
</tbody>
</table>


Incidence of overt hypothyroidism in 20 years of followup (n=1877) in patients with subclinical hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.6/1000/yr</td>
<td>4.1/1000/yr</td>
</tr>
</tbody>
</table>

Risk was increased in patients with thyroid autoantibodies


Symptom score (cramps, dry skin, cold intolerance, constipation, fatigue)

Symptom score higher in subclinical hypothyroid patients

Lipids

Increased LDL chol

Cardiovascular

Slowed myocardial relaxation and impaired LV diastolic filling
Increased systemic vascular resistance
Impaired endothelial function
Effect of Lthyroxine therapy on LDL-cholesterol levels. Double blind placebo controlled study

Monzani et al. JCEM 89:2099 (2004)

Lthyroxine replacement in subclinical hypothyroidism

Small placebo controlled studies have shown:

a. Improvement in symptom score
b. Improvement in diastolic function
c. Majority of studies show improvement in total cholesterol and LDL cholesterol

Clinical case

72 year old African American man referred for evaluation of multinodular goiter

History of paroxysmal atrial fibrillation dating back to 1970’s. Treated with amiodarone from 2007 to 2009. Also has history of panic attacks

Low TSH values for the past 10 yrs

TSH 0.1; FT4 20; FT3 199, negative TPO antibody

Serum TSH elevated
Normal FT4 and FT3

TSH 4.5 – 10 mIU/L
Rx with T4 if:
Planning pregnancy
Thyroid disease – positive abs; thyroiditis on US; goiter; symptoms

TSH > 10 mIU/L
Give T4

Blond and Cooper Endo Rev 26:76 (2008)
**Prevalence of subclinical hyperthyroidism in patients not on thyroid meds**

<table>
<thead>
<tr>
<th>TSH</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado state fair</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>NHANESIII</td>
<td>&lt;0.4</td>
</tr>
</tbody>
</table>

Subclinical hyperthyroidism may progress to overt hyperthyroidism

Progression depends on serum TSH and etiology

If TSH < 0.1, progression to overt hyperthyroidism is 2 to 5% per year

Subclinical Graves’ (TSI positive) more likely to normalize than multinodular goiter

Woeber Thyroid 15:687 (2005); Parle et al Lancet 358:861 (2001)

Associated with increased risk of AF in Framingham cohort during 10 year followup


**Meta-analysis: 9 to 10 year change in bone mass in pre- and post-menopausal women with suppressed TSH levels due to Lthyroxine treatment compared to controls**

**Suppressed TSH is associated with increased risk of fractures**

65 year old women with exogenous or endogenous subclinical hyperthyroidism have increased risk of hip and vertebral fracture when compared to women with normal thyroid hormone levels.


**Effect of methimazole therapy on 10 patients with subclinical hyperthyroidism**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 6 months of methimazole therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>0.05</td>
<td>1.4</td>
</tr>
<tr>
<td>Pulse</td>
<td>81.5</td>
<td>73.5</td>
</tr>
<tr>
<td># atrial premature beats/24 hr</td>
<td>86.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Ventricular premature beats/24h</td>
<td>8.0</td>
<td>0</td>
</tr>
<tr>
<td>LV mass index (g/m2)</td>
<td>89.7</td>
<td>71.5</td>
</tr>
</tbody>
</table>


**Cardioversion attempted and unsuccessful in 3**

1 patient treated with carbimazole; 3 treated with $^{131}$I

Forter et al. Int J Cardiol 143:1981

**Postmenpausal women with multinodular goiter and treated subclinical hyperthyroidism had stable bone density over 2 years whereas those untreated had 2% bone loss**

Faber et al. Clin Endocrinol 48: 285 (1998);
Persistently low TSH; normal FT4; T3

Evaluate for thyroid disorders (u/s; uptake and scan; TSI)

Postmenopausal; age > 60, history of AF or heart disease, osteoporosis; symptoms

TSH < 0.1 to 0.4

Rx with $^{131}$I or thionamides

age < 60; premenopausal; healthy; no symptoms

TSH < 0.1

optional

TSH 0.1 to 0.4

No Rx

Clinical case

31 year old woman presented with amenorrhoea

TSH 16.1

Started on T4 50 µg/day; and over next 6 months because her TSH levels remain elevated (16,13,14,16), T4 dose gradually increased to 175 µg/day

− Saw an endocrinologist in Taiwan complaining of anxiety, racing heart beat, fatigue

TFT panel

TSH 17 µIU/mL (0.35-5.5)
Total T4 29 µg/dL (4.5-10.9)
Total T3 13.4 ng/mL (0.6-1.8)

The T4 was discontinued

2 weeks later

TSH 17.8 (0.35-5.5)
TT4 19.7 (4.5-10.9)
TT3 3.67 (0.6-1.8)
FrT4 3.22 (0.89-1.8)
Clinical case

37 year old man with type 1 diabetes, Graves’ disease and Graves’ ophthalmopathy
Treated with methimazole for ~ 4 years; relapsed on stopping the drug
Underwent total thyroidectomy
Pathology – multifocal papillary thyroid cancer – 0.2 cm and 0.3 cm lesion in left lobe; 0.5 cm lesion right lobe
Positive for BRAF mutation

Age 45; > 1cm lesion; multicentric or invasive

Initial treatment - induction of remission
Total thyroidectomy and modified neck dissection if evidence for LN involvement
After recovery, ablation of thyroid remnant with $^{131}I$ either following thyroxine withdrawal or recombinant TSH stimulation

Lthyroxine treatment; long term surveillance
Serial ultrasounds and thyroglobulin measurements following thyroxine withdrawal or recombinant TSH stimulation. Surgery and/or $^{131}I$ for recurrent disease

Thyroxine withdrawal Protocol
1. Stop T4
2. 25 to 50 ug T3 for 4 wks
3. Stop T3 and go on low iodine diet for 2 wks
4. $^{131}I$ Rx
5. Restart T4 2 days after Rx

Recombinant TSH Protocol
1. Low iodine diet for 2 wks
2. Stop T4 two days before 1st RhTSH injection
3. RhTSH injections 2 consecutive days
4. $^{131}I$ following day
5. Restart T4 3 days after Rx
Preparation with RhTSH vs T4 withdrawal for remnant ablation
With 100 mCi 131I in low risk differentiated thyroid CA – 3.5 year follow-up

<table>
<thead>
<tr>
<th></th>
<th>After T4 withdrawal</th>
<th>After TSH injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>No 131I uptake</td>
<td>17/18 (94%)</td>
<td>21/25 (84%)</td>
</tr>
<tr>
<td>Tg &lt; 2 ng/ml</td>
<td>19/20 (95%)</td>
<td>24/25 (96%)</td>
</tr>
</tbody>
</table>

* Recombinant TSH costs $2500
Elisei et al. JCEM 94: 4171, 2009

Effective half life (physical decay plus biological disappearance) of 131I after rhTSH vs LT4 withdrawal

Extrathyroidal tissue radiation damage is less with rhTSH preparation than with T4 withdrawal

Age 45; > 1cm lesion; multicentric or invasive

Initial treatment - induction of remission
Total thyroidectomy and modified neck dissection if evidence for LN involvement
After recovery, ablation of thyroid remnant with 131I either following thyroxine withdrawal or recombinant TSH stimulation

Lthyroxine treatment; long term surveillance
Serial ultrasounds and thyroglobulin measurements following thyroxine withdrawal or recombinant TSH stimulation. Surgery and/or 131I for recurrent disease
1 μg of thyroid tissue results in serum Tg < 1 μg/l when TSH in normal range & 0.5 μg/l when TSH suppressed

Haugen et al. JCEM 84:3877 (1999)

<table>
<thead>
<tr>
<th>Tg level</th>
<th>Tg level &gt; 0.1 μg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>True negative (152)</td>
<td>137</td>
</tr>
<tr>
<td>True Positive (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Positive predictive value 100%; negative predictive value is 90%


Constitutive activation of MAP kinase/ERK pathway occurs in 80% of papillary thyroid CA

- BRAF activating mutations occur in ~45% PTC
- Fusion RET protein—replacement of extracellular domain of RET by RET-fused genes leading to constitutive ligand-independent activation of RET kinase. 20% of PTC. More common in ionizing and childhood cancers.
- RAS mutations more likely to occur in follicular variant of PTC; familial thyroid CA
Odds ratios for PTC recurrence with BRAF mutation (overall = 2.71)

- Xing et al, 2005
- Kim et al, 2006
- Riesco-Eizaguirre et al, 2006
- Kebebew et al, 2007
- Abubaker et al, 2008
- Elisei et al, 2008
- Xing et al, 2009
- All Studies

Survival probability of PTC patients

- BRAF-
- BRAF+
- P = 0.015

Follow-up Time (years)

Survival Probability (%)

Molecules targeting thyroid specific oncogenic kinases

Use in patients with progressive $^{131}$I resistant disease

- PLX4032 – small molecule inhibitor of BRAF

- Multikinase inhibitors – Sorafenib, sunitinib, motesanib, axitinib, vandetanib, XL184

- Sorafenib (BRAF, VEGFR) in phase 2 studies show about ~75% had partial response (at least 30% decrease in diameter after 4 wks) or stable disease (< 30% decrease or < 20% increase)

- Significant side effects – fatigue, hypertension, prolonged QT interval, thromboembolism, diarrhea, nausea, perforation, hard foot syndrome, rash, stomatitis, photosensitivity, keratoacanthomas, squamous cell CA