23 Year Old Female presented with resistant hypothyroidism

Endorama 01/09/2014
Milad Abusag MD
First year fellow
HPI

• 23 year old F with PMH of hypothyroidism, and obesity
• Hypothyroidism diagnosed 7 years ago
• Initially treated with Synthroid 75 mcg/day
• Doing well until 2 year ago
  – worsening fatigue, constipation, dry skin, hair loss and Wt gain (20 pounds over the past 6 months)
  – PCP had a very difficult time finding the appropriate dose her thyroid hormone
  – Tried on different thyroid medication (Synthroid, Levoxyl, Tirosint)
  – Thyroid hormones dose increased gradually to 325 mcg daily without response.
• Had a h/o chronic diarrhea, (2-3 bowel movements every day), no steatorrhea.
• Underwent extensive work up including colonoscopy twice, celiac panel and all negative
• **PMH:**
  ✓ Hypothyroidism
  ✓ Acne
  ✓ Chronic diarrhea

• **Family History:**
  ✓ Hypothyroidism (maternal grandmother)
  ✓ HLD mother

• **Surgical history:** Non

• **Social history**
  ✓ Never smoke, drink alcohol socially, no illicit drugs.

• **Home medications**
  ✓ Synthroid 325 mcg daily
  ✓ Doxycycline 100 mg daily
  ✓ OCP
ROS

- **Constitutional**: fatigue, Wt gain, no change in the appetite
- **HENT**: Headache, blurred vision, No sore throat
- **Neck**: supple, no thyromegaly, no nodules, no LD.
- **Cardio/pulm**: No CP, no palpitation, no orthopnea or PND
- **GI**: No pain, + diarrhea, no vomiting, no melena or hematochezia
- **GU**: Negative
- **Skin/MSK**: dry skin, increasing hair loss, no rash, no striae
- **Neuro**: no headache, no weakness, no numbness, no tingling,
- **Psych**: negative
On Examination

- **Vitals:** BP 114/77 | Pulse 85, no fever, RR 14. Wt 127kg, BMI 49
- **General:** Obese, awake alert, setting comfortable on exam table
- **HEENT:** normocephalic non traumatic, no plethora, no supraclavicular fullness, EOM normal
- **Neck:** supple, no LN enlargement, no thyromegaly, no acanthosis nigricans
- **CVS/Pulm:** clear equal air entry no added sounds, S1 + S2, no murmur.
- **Abd:** soft lax, no organomegaly, no tenderness, audible bowel sounds.
- **Skin:** warm, no rash, no acanthosis nigricans, no striae
- **Neuro:** CN intact, sensation normal, normal reflexes
- **Psych:** normal mood, and affect
## General labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Normal</td>
</tr>
<tr>
<td>Glucose</td>
<td>75</td>
</tr>
<tr>
<td>HbA1c</td>
<td>4.5</td>
</tr>
<tr>
<td>K</td>
<td>4.4</td>
</tr>
<tr>
<td>Carbon Dioxide</td>
<td>26</td>
</tr>
<tr>
<td>Anion gap</td>
<td>13</td>
</tr>
<tr>
<td>BUN</td>
<td>18</td>
</tr>
<tr>
<td>Cr</td>
<td>0.7</td>
</tr>
<tr>
<td>GFR (Calc)</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Ca</td>
<td>8.7</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1</td>
</tr>
<tr>
<td>ALT</td>
<td>17</td>
</tr>
<tr>
<td>AST</td>
<td>28</td>
</tr>
<tr>
<td>ALP</td>
<td>69</td>
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# TFT from outside facility

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (0.4 – 4.5)</td>
<td>10.8</td>
<td>7.28</td>
<td>8.6</td>
<td>9.32</td>
<td>41.4</td>
<td>11.2</td>
</tr>
<tr>
<td>FT4 (0.8 – 1.8)</td>
<td>0.9</td>
<td>1.07</td>
<td>1.04</td>
<td>0.92</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>FT3 (2.3 – 4.2)</td>
<td>4.53</td>
<td>4.16</td>
<td>4.48</td>
<td>4.4</td>
<td>3.38</td>
<td></td>
</tr>
</tbody>
</table>

The TFT from an outside facility:

<table>
<thead>
<tr>
<th>Test/date</th>
<th>1/2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPO Ab (&lt;35)</td>
<td>47</td>
</tr>
<tr>
<td>24hrs urine cortisol</td>
<td>56 (no ref range available for that lab)</td>
</tr>
<tr>
<td>Celiac panel</td>
<td>Negative</td>
</tr>
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</table>
# Ultrasound studies

<table>
<thead>
<tr>
<th>Date/study</th>
<th>Rt lobe</th>
<th>Lt lobe</th>
<th>Isthmus</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/2006</td>
<td>5.3 x 1.7 x 1.5 cm</td>
<td>5 x 1.7 x 1.4 cm</td>
<td>0.4 cm</td>
</tr>
<tr>
<td>This visit</td>
<td>3.95 x 1.59 x 1.4</td>
<td>3.79 x 1.47 x 1.41 cm</td>
<td>0.38 cm</td>
</tr>
</tbody>
</table>

*Heterogeneity suggesting hashimoto’s*
## Thyroxine absorption test

<table>
<thead>
<tr>
<th>Test/elapsed time</th>
<th>0</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>240 min</th>
<th>360 min</th>
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</thead>
<tbody>
<tr>
<td>T4</td>
<td>11.1</td>
<td>13.1</td>
<td>18.4</td>
<td>17.3</td>
<td>17.8</td>
<td>17.4</td>
</tr>
<tr>
<td>TSH</td>
<td>5.61</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Clinical Qs

1. What is the indications to do an absorption test
2. How does one interpret the results
3. Would weekly LT4 administration be an alternative for the treatment of noncompliance?
Pseudomalabsorption of Levothyroxine

Kenneth B. Ain, MD; Samuel Refetoff, MD; Henry G. Fein, MD; Bruce D. Weintraub, MD

Objective.—The issue of patient compliance with pharmacological therapy vs malabsorption of medication was explored in the context of persistent hypothyr-roidism despite the administration of large doses of levothyroxine sodium.

Setting.—Referral care in two large tertiary care centers.

Patients.—Four patients, seen within two decades, with clinical and biochemical hypothyroidism while receiving levothyroxine, were evaluated for selective malabsorption of this hormone. 

Interventions.—Studies included serial measurements of thyroid hormone levels after a loading dose of levothyroxine or liothyronine sodium or evaluation with a double-labeled thyroxine tracer technique. Results were compared with studies of levothyroxine malabsorption in the medical literature.

Results.—All patients were ultimately found to have normal (82% to 100%) absorption of oral levothyroxine. There was no evidence that malabsorption of levothyroxine could occur as an isolated abnormality.

Conclusions.—Some patients exhibit a factitious disorder suggesting malab- sorption of levothyroxine. When treating hypothyroidism, psychiatric issues may result in noncompliance with levothyroxine therapy.

LEVOTHYROXINE sodium is the most commonly used thyroid hormone preparation for treating hypothyroid- ism. Older studies showed the mean daily thyroxine (T<sub>4</sub>) hormone replacement therapy to be 109 ± 66 μg (2.28 ± 1.57 μg/kg body weight) prior to a reformulation of a major brand in 1982. Evaluation of the current levothyroxine formulation yielded a mean daily replacement dose of 112 ± 15 μg (1.36 ± 0.42 μg/kg body weight) and demonstrated absorption from the gastroin-testinal tract at approximately 81% of the administered oral dose.

Patients may be seen with clinical or biochemical evidence of hypothyroidism despite concurrent therapy with a high dose of levothyroxine. If free serum thyroxine (T<sub>4</sub>) levels are elevated in association with inappropriately elevated serum thyrotropin (thyroid-stimu-lating hormone [TSH]) levels, the syndrome of thyroid hormone resistance or thyrotropin-secreting pituitary tumors should be considered. More often, the free T<sub>4</sub> level is low, with an appropriate elevation of thyrotropin levels. In this situation, the patient may be poorly compliant in taking levothyroxine or be misdiagnosing the medication. When it appears likely that levothyroxine has been reliably ingested, factors affecting absorption should be considered.

We evaluated four patients because of low free serum T<sub>4</sub> levels, elevated thyrotropin levels, and symptoms of hypothyroidism despite therapy with up to eightfold the mean daily dose of levothyroxine. In each case, studies ultimately documented normal absorption of levothyroxine.

Methods

Studies of levothyroxine and liothy- ronine absorption were performed after receiving informed consent from each of the subjects. Patients A, B, and D received liothyronine sodium (Synthroid, Flint Laboratories Inc, Deerfield, Ill) given in five to ten 200-μg tablets at a single time. Additionally, patients A and B received 100- and 75-μg oral doses, respectively, of liothyronine sodium (Cytomel, Smith Kline & French Laboratories, Philadelphia, Pa), and levothyroxine in a liquid form (parenteral Synthroid in normal saline with 1.0% human serum albumin). Serial blood samples were obtained for hormone assays, before and after the administration of levothyroxine or liothyronine, for up to 24 hours. Liothyronine absorption data on normal and hypothyroid control subjects were obtained during a previous study. Levothyroxine test-dose ingestion was finally verified in each patient by careful observation of oral administration and monitoring for surreptitious regurgitation. Patient A permitted visual and digital examination of her oral cavity, while patient B consented to placement of a nasogastric tube for instillation of crushed levothyroxine tablets.

Absorption of oral levothyroxine in patient C was studied by an indication of the method of Hays. Ten microcuries of levothyroxine I 125 in 1% human serum albumin (Lederle Laboratories, Pearl River, NY) was ingested orally at the same time as 10 μCi of levothyroxine I 131 in 1% human serum albumin was injected intravenously. The ratio of 125<sup>I</sup> to 131<sup>I</sup> activity in serum samples obtained over 24 hours determined absorption of the oral levothyroxine.

Patient Reports and Results

Patient A.—Patient A was a 49-year-old female nursing assistant referred in 1985 for hypothyroidism. Therapy had started with 125 μg of levothyroxine sodium daily at 23 years of age. The levothyroxine sodium dose had been recently increased to 175 μg/day because of a thyrotropin level of 40 mU/L (normal, 0.5 to 4.0 mU/L) with hypothyroid symptoms. Persistent hypothyroidism had necessitated a further increase of levothyroxine to 400 μg/d, resulting in a thyrotropin level of 64 to 154 nmol/L (normal, 7.7 to 12.5), and thyrotropin level of 15.9 mU/L. His history was significant for multiple medical, psychiatric, and surgical interventions.

A levothyroxine absorption study (Figure, A) was performed with 1.0 mg...
A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment

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- Department of Endocrinology, Oxford University Hospitals NHS Trust, OCDEM, Oxford OX3 7LJ, UK and ¹Department of Endocrinology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

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Study design

- Using 1 mg Levothyroxine bolus dose followed by a weight-determined oral L-T₄ weekly bolus, absorption was assessed in 23 patients.
- Patients were identified who despite the treatment with an adequate daily dose of L-T₄ (daily dose 1.6 mcg/kg per day) had failed to be rendered.
- None of the selected patients were on drugs known to interfere with L-T₄ absorption/clearance and none were pregnant.
- All patients had a confirmed negative coeliac antibody screen and patients with known malabsorptive pathology were excluded.
- No patient had a history of cardiac disease.
120 minutes absorption response

Figure 1 Thyroxine (T₄) absorption test demonstrating the significant rise in free T₄ after a weight-related bolus of T₄ (n=23; mean ± s.d.; ***P<0.0001).

- **In normal subject** T₄ level should increase by more than 54%.
Response to weekly dose of Wt based T4

Figure 2: Levothyroxine (L-T4) dose and TSH value pre- and post-study showing a significant reduction in TSH (white boxes; mean ± s.d.: *P < 0.05) despite a significant reduction in the L-T4 dose (black boxes; mean ± s.d.: **P < 0.005) for patients in whom their TSH improved (n=17).

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Conclusion

- All patients showed a rise in fT₄ at 120 min following the administration of the L-T₄ bolus, with a mean increase of 54% from baseline.
- Following the treatment period, using an Wt based weekly L-T₄ dose, TSH reduced from baseline in 75% of cases ((17/23 patients the mean TSH had reduced from 47.1 to 17.6))
Data for the six patients in whom their TSH remained elevated following the administration of a weight-related weekly levothyroxine dose

<table>
<thead>
<tr>
<th>Patient</th>
<th>T4 baseline</th>
<th>T4 120min</th>
<th>TSH baseline</th>
<th>4wks TSH</th>
<th>T4 dose (mcg/kg/d)</th>
<th>T4 dose pretest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.3</td>
<td>22.6</td>
<td>12</td>
<td>21</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>16.5</td>
<td>30.8</td>
<td>17</td>
<td>23</td>
<td>1.6</td>
<td>1.87</td>
</tr>
<tr>
<td>3</td>
<td>14.8</td>
<td>30.4</td>
<td>33</td>
<td>53</td>
<td>1.6</td>
<td>2.85</td>
</tr>
<tr>
<td>4</td>
<td>16.5</td>
<td>26.9</td>
<td>19.9</td>
<td>24.6</td>
<td>1.6</td>
<td>1.95</td>
</tr>
<tr>
<td>5</td>
<td>17.8</td>
<td>29.7</td>
<td>55</td>
<td>72</td>
<td>1.6</td>
<td>2.54</td>
</tr>
<tr>
<td>6</td>
<td>16.2</td>
<td>25</td>
<td>10.2</td>
<td>37.5</td>
<td>1.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Note: in the study they did not specifically ask about grapefruit juice or ingestion of soy protein supplements, both of which have been shown to affect absorption

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Back to my patient

• Advised to go back to her previous dose.
• Repeat TFT in 8 weeks (due this week).
Take home points

- Patients who are receiving doses of levothyroxine of more than 2 μg/kg of body weight, with persistently increased thyroid-stimulating hormone levels, should undergo testing for malabsorption and pseudomalabsorption of levothyroxine.

- Before proceed with T4 absorption test we need to exclude secondary causes of malabsorption such as medication interference, dietary interference, intraluminal bacterial overgrowth, CHF, and Celiac disease.

- Rise in FT₄ bolus by >54% from baseline at 120 min following the administration of the L-T₄ considered positive result in most of the studies.
References


Thank you