23 Year Old Female presented with resistant hypothyroidism

Endorama 01/09/2014

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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 (20pounds 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

Test	Result
CBC	Normal
Glucose	75
HbA1c	4.5
K	4.4
Carbon Dioxide	26
Anion gap	13
BUN	18
Cr	0.7
GFR (Calc)	>90
Ca	8.7
Albumin	4.1
ALT	17
AST	28
ALP	69

TFT from outside facility

Test/date	5/2012	8/2012	11/2012	1/2013	3/2013	7/2013
TSH (0.4 – 4.5)	10.8	7.28	8.6	9.32	41.4	11.2
FT4 (0.8 – 1.8)	0.9	1.07	1.04	0.92	0.7	0.9
FT3 (2.3 – 4.2)		4.53	4.16	4.48	4.4	3.38
		200 mcg	225 mcg	275 mcg	300 mcg	325 mcg

Test/date	1/2013
TPO Ab (<35)	47
24hrs urine cortisol	56 (no ref range available for that lab)
Celiac panel	Negative

Ultrasound studies

Date/study	Rt lobe	Lt lobe	Isthmus
3/2006	5.3 x 1.7 x 1.5 cm	5 x 1.7 x 1.4 cm	0.4 cm
This visit	3.95 x 1.59 x 1.4	3.79 x 1.47 x 1.41 cm	0.38 cm

Heterogeneity suggesting hashimoto's

Thyroxine absorption test

Test/elapsed time	0	60 min	120 min	180 min	240 min	360 min
T4	11.1	13.1	18.4	17.3	17.8	17.4
TSH	5.61					

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?

Brief Report

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 hypothyroidism despite the administration of large doses of levothyroxine sodium.

Design.—Retrospective case series.

Setting.—Referred 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 can occur as an isolated abnormality.

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

(*JAMA*. 1991;266:2118-2120)

LEVOTHYROXINE sodium is the most commonly used thyroid hormone preparation for treating hypothyroidism. Older studies showed the mean daily dose for thyroid hormone replacement therapy to be 169 ± 66 μg (2.25 ± 0.67 μg/kg of body weight)[1] prior to a reformulation of a major brand in 1982.[2,3] Evaluation of the current levothyroxine formulation yielded a mean daily replacement dose of 112 ± 19 μg (1.63 ± 0.42 μg/kg of body weight) and demonstrated absorption from the gastrointestinal tract at approximately 81% of the administered oral dose.[4]

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_4) levels are elevated, in association with inappropriately elevated serum thyrotropin (thyroid-stimulating hormone [TSH]) levels, the syndrome of thyroid hormone resistance or thyrotropin-secreting pituitary tumors should be considered.[5] More often, the free T_4 level is low, with an appropriate elevation of thyrotropin levels. In this situation, the patient may be poorly compliant in taking levothyroxine or be malabsorbing 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_4 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 liothyronine absorption were performed after receiving informed consent from each of the subjects. Patients A, B, and D received 1.0 to 2.0 mg of levothyroxine 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.[6] Liothyronine absorption data on normal and hypothyroid control subjects were obtained during a previous study.[7] 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 using a modification of the method of Hays.[8] 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}I to ^{131}I 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 200 μg/d because of a thyrotropin level of 40 mU/L (normal, 0.5 to 4.0 mU/L) with hypothyroid symptoms. Persistent symptoms had necessitated a further increase of levothyroxine to 400 μg/d, resulting in a serum T_4 level of 81 nmol/L (normal, 64 to 154 nmol/L), free T_4 index of 56.6 (normal, 77 to 135), and thyrotropin level of 5.9 mU/L. Her history was significant for multiple medical, psychiatric, and surgical interventions.

A levothyroxine absorption study (Figure, A) was performed with 1.0 mg

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the opinions of the Department of the Army or the Department of Defense.

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A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non-adherence to treatment

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Study design

- Using 1 mg Levothyroxine bolus dose followed by a weight-determined oral L-T_4 weekly bolus, absorption was assessed in 23 patients.
- Patients were identified who despite the treatment with an adequate daily dose of L-T_4 (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-T_4 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.

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120 minutes absorption response

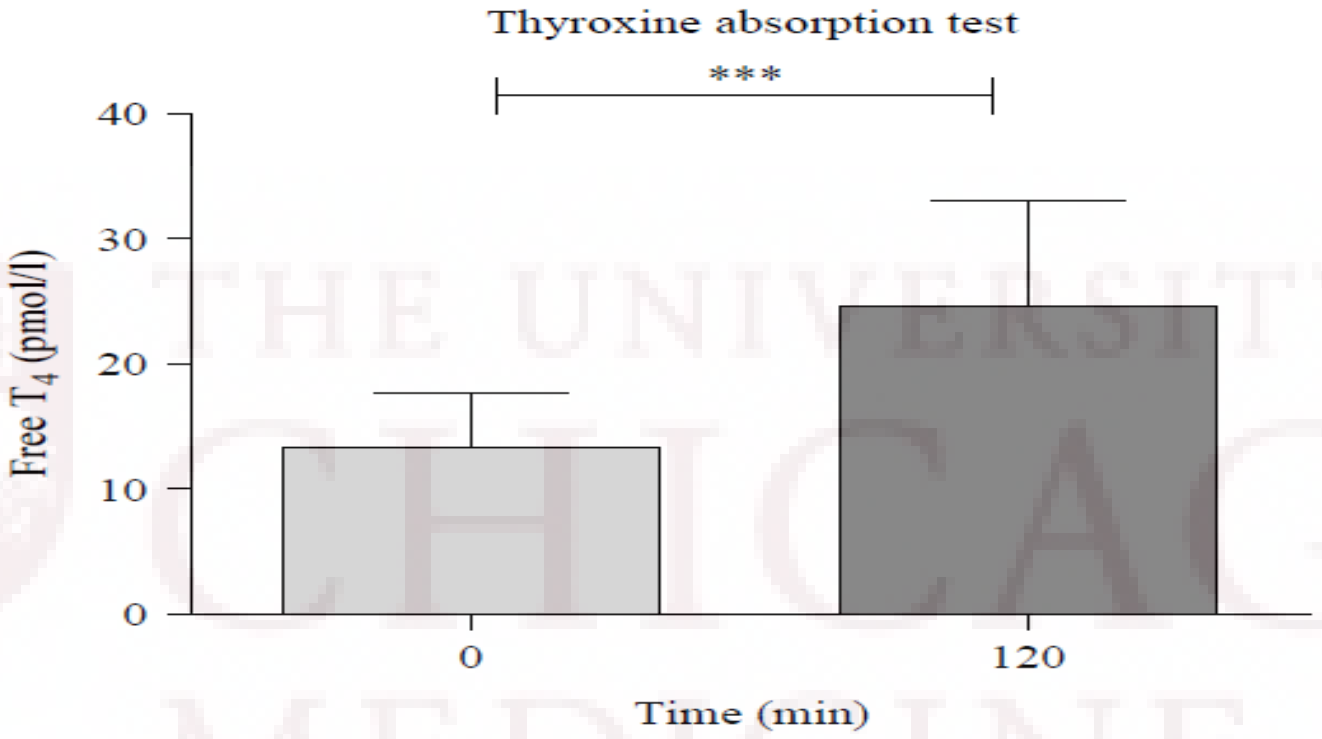

Figure 1 Thyroxine (T_4) absorption test demonstrating the significant rise in free T_4 after a weight-related bolus of T_4 ($n=23$; mean+S.D.; $^{***}P<0.0001$).

- **In normal subject T4 level should increase by more than 54%.**

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Response to weekly dose of Wt based T4

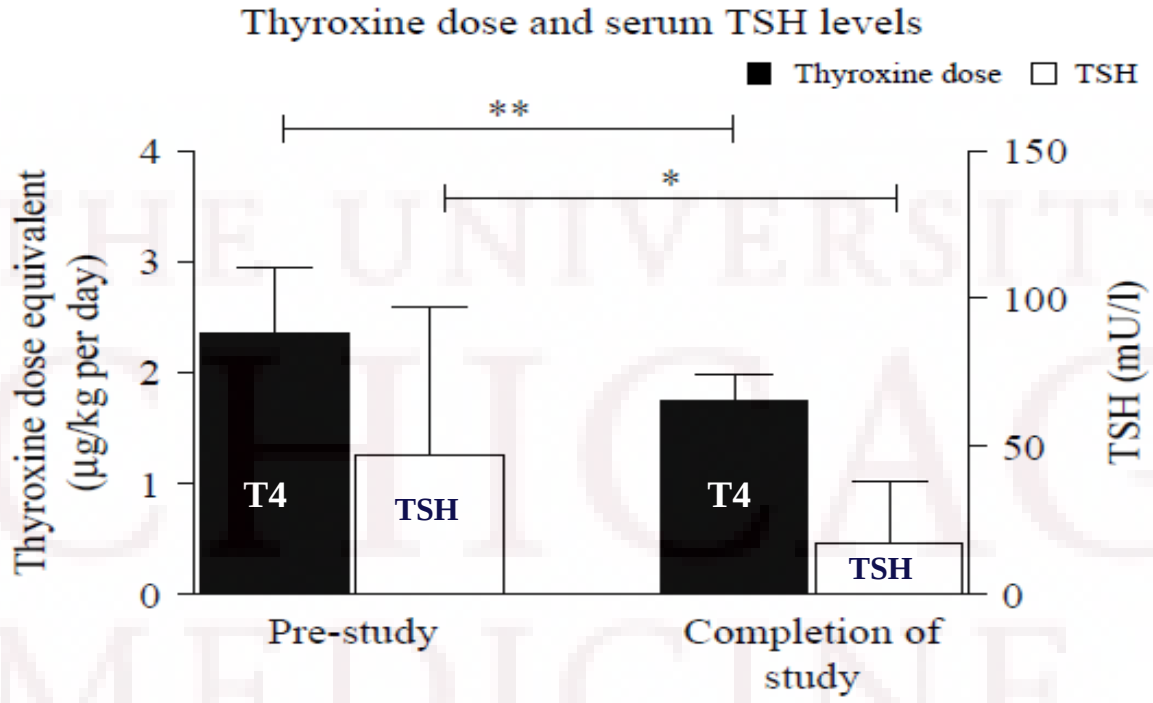

Figure 2 Levothyroxine (L-T_4) dose and TSH value pre- and post-study showing a significant reduction in TSH (white boxes; mean+S.D.: $^{*}P<0.05$) despite a significant reduction in the L-T_4 dose (black boxes; mean+S.D.: $^{**}P<0.005$) for patients in whom their TSH improved ($n=17$).

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Conclusion

- All patients showed a rise in fT_4 at 120 min following the administration of the L-T_4 bolus, with a mean increase of *54% from baseline*
- Following the treatment period, using an Wt based weekly L-T_4 dose, **TSH reduced from baseline in 75% of cases** ((17/23 patients the mean TSH had reduced from 47.1 to 17.6))

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- ✓ **Data for the six patients in whom their TSH remained elevated following the administration of a weight-related weekly levothyroxine dose**

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

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 FT_4 bolus by >54% from baseline at 120 min following the administration of the L-T_4 considered positive result in most of the studies.

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Thank you