A 75 year old woman with weight loss

- A 75 year old woman presents with 10 lb weight loss over the past 2 months. Her appetite has been good, she denies early satiety or other GI symptoms. She has a history of a “heart problem” for which she has been taking 3 medications for the past 6 months. Her only other symptom is increased difficulty with her handwriting because of shaking when she attempts to write.
Physical Examination

- Height 5' 4"
- Weight 140 lbs
- BP 140/70 Pulse 100/min regular
- Thyroid normal size and consistency
- Heart regular rate and rhythm
- Lid lag, otherwise eye exam normal
- Skin normal
- No myopathy but she has a tremor bilaterally

All of the following would be appropriate except

1. Obtain previous records
2. CBC
3. Chem 7
4. Ultrasensitive TSH
5. Chest and Abdominal CT

Further History

- Treated for atrial fibrillation 9 months ago with cardioversion.
- Medications:
  - Amiodarone 100mg qd
  - Aspirin
  - Lisinopril
Current Laboratory Values

- TSH < 0.01 mIU/ml
- CBC normal
- SMA 12 normal

WHAT DOES THE TSH LEVEL MEAN?

<table>
<thead>
<tr>
<th>TSH Level</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.01</td>
<td>hyperthyroid</td>
</tr>
<tr>
<td>0.1-0.4</td>
<td>hyperthyroid (sub-clinical)</td>
</tr>
<tr>
<td>0.4-4.0</td>
<td>euthyroid</td>
</tr>
<tr>
<td>&gt; 4.0</td>
<td>hypothyroid</td>
</tr>
</tbody>
</table>

What would you do next?

1. Thyroid ultrasound study
2. Obtain anti-thyroid antibodies
3. Obtain thyroid hormone levels
4. I-123 thyroid uptake and scan
Results of laboratory tests:
- Free T4 = 2.8 ng/dL (normal 0.8 – 1.9)
- Total T4 = 12 ug/dL (normal 5-10)
- Total T3 = 130 ng/dL (normal 80 – 180)
- T3RU - normal

What would you do next?
1. Begin anti-thyroid medications
2. Begin prednisone
3. Ask the patient to bring in her meds for your own review
4. Obtain an I-123 thyroid uptake and scan

DISORDERS OF THYROTOXICOSIS

Radioactive Iodine Uptake (RAIU)

- Increased
  - Graves' Disease
  - hCG
  - Hot Nodule
  - Multinodular Goiter
  - TSH-induced
- Absent
  - Thyroiditis
  - Iodine
  - Exogenous
  - Struma Ovarii
  - Thyroid Cancer

Low Iodine Uptake in Patient with Thyroiditis

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24 hours Post-RAI

24 hour I-123 uptake is 1% (normal 5 – 35)
The most likely diagnosis at this time is?

1. Graves’ disease
2. Amiodarone induced hyperthyroidism
3. Toxic nodule
4. Subacute thyroiditis

Amiodarone and the Thyroid

Amiodarone contains significant iodine (10 times the normal daily intake/100 mg dose).
Also blocks T4 to T3 conversion and T3 action.
- May cause hyper- or hypothyroidism
- Amiodarone induced thyrotoxicosis can be severe

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Regarding treatment all of the following may be appropriate except:

1. Methimazole
2. I-131
3. β blockers
4. Prednisone
5. Perchlorate

Treatment

• Think about stopping amiodarone if possible
• Symptomatic - beta blockers
• Antithyroid drugs
• Steroids for thyroiditis
• Surgery if amiodarone cannot be stopped and no response to medical therapy

My Approach: methimazole and prednisone 10 bid

A 45 year old man with hypercalcemia

An asymptomatic 45 year old man presents for the first time for the evaluation of recently discovered hypercalcemia (11.6 mg/dL [normal 9 – 10.5 mg/dL]). He reports a 1-2 yr history of hypertension treated with hydrochlorothiazide 25 mg/day. There is no history of renal stones or fractures. His BP is 130/82. His physical examination is normal.
All of the following additional information would be appropriate at this stage, except:

1. Chest X Ray
2. Serum ACE level
3. Chem 7, serum albumin, phosphate
4. Previous serum calcium values

Laboratory test results reveal the following:

- Na 141 mEq/L
- K 3.7 mEq/L
- CO₂ 22 mEq/L
- Cr 0.9 mg/dl
- Albumin 4.0 g/dl
- Ca 11.6 mg/dL (normal 9 – 10.5)
- Ionized calcium 1.67 mmol/L (nl 1.12-1.23)
- PO₄ 2.3 mg/dL (normal 2.7 - 4.5)
- Chest x-ray normal
- No prior Ca available

Manifestations of Hypercalcemia

- CNS dysfunction
- Muscle weakness
- Bowel hypomotility and constipation
- ? Peptic ulcer disease
- Pancreatitis
- Renal insufficiency
- Nephrolithiasis
- Nephrogenic diabetes insipidus
- Corneal calcium deposition (band keratopathy)
- Shortening of QT interval
What would be the most appropriate next step?

1. Discontinue hydrochlorothiazide, repeat calcium measurement, measure PTH
2. Stop hydrochlorothiazide and measure PTH
3. Obtain serum PTH
4. Obtain a 24 hr urine calcium

Hydrochlorothiazide was discontinued.

PTH 60 pg/ml (Normal 10 - 65).
Repeat serum Ca 11.8 mg/dL
BP at follow up is 140/92.

The most likely diagnosis is:

1. Familial hypocalciuric hypercalcemia (FHH)
2. Sarcoidosis
3. Primary hyperparathyroidism
4. Humoral hypercalcemia of malignancy
Classic Biochemical Features of Primary Hyperparathyroidism

- Hypercalcemia
- Hypophosphatemia
- Hyperchloremic acidosis
- Elevated alkaline phosphatase
- Inappropriately normal or elevated serum PTH
- Normal or elevated urinary calcium

Primary Hyperparathyroidism - Etiology

![Diagram showing calcium sensing receptor (CaR) and pathways to bones, kidneys, and other tissues]

- Calcium sensing receptor (CaR)
  - FHH (inactivating)
  - Autosomal Dominant Hypocalcemia (activating)

Common Causes of Hypercalcemia

- PTH Related
  - Primary hyperparathyroidism
  - Familial hypocalciuric hypercalcemia
  - Malignancy
    - Solid tumors-PTHrP

- Non-PTH Related
  - Malignancy
  - Granulomatous disease
  - Hyperthyroidism
  - Thiazide diuretics
  - Vitamin D intoxication
  - Addison's disease
All of the following would be appropriate, except:

1. Referral for parathyroidectomy
2. Measure bone mineral density
3. Keep patient off hydrochlorothiazide and follow
4. Obtain a Tc-99m sestamibi imaging study
5. Measure 24 hr urine calcium excretion

24 hour urine calcium was 410mg*. In addition a plain x ray of the abdomen revealed nephrocalcinosis.

*Normal urine calcium excretion depends on dietary calcium intake
*Usually less than 300 mg/day
Primary Hyperparathyroidism - Treatment

NIH Consensus: Indications for Surgery

- Serum calcium > 1 mg/dL above normal
- Visible or history of nephrolithiasis
- Decreased bone mineral density
  - Reduced by more than 2.5 SD below peak bone density.
- Decreased creatinine clearance
- Age less than 50 years

Primary Hyperparathyroidism: Additional Indications for Surgery

- Patient prefers surgery
- Consistent follow up unlikely
- Coexistent illness complicates management

Primary Hyperparathyroidism: Who should be monitored?

- Patients above 50 yrs whose biochemical disease is not severe and who have no evidence of complications of hyperparathyroidism
- Patients who are poor operative risks or extremely frail or elderly
Primary Hyperparathyroidism: Ongoing Monitoring

- Semiannual then annual follow up with measurement of:
  - BP
  - Serum Ca
  - Serum creatinine (with creatinine clearance if indicated)
  - Abdominal radiograph annually
  - Bone mineral density annually
  - Urine Ca in selected patients

Primary Hyperparathyroidism - Treatment

A New Option - Calcimimetic (Cinacalcet)

Ca++ \( \rightarrow \) PTH

\[ \text{Peacock et al, 2005: JCEM} \]

\[ \text{Peacock et al, 2011: JCEM} \]

An Incidental Thyroid Nodule

A 45 year old man is found to have a 2.0 cm nodule in his left thyroid lobe – discovered when a MRI scan was performed for neck pain. His Past Medical History is unremarkable. His Family History is negative. He is currently on no medications.

On further questioning there is no history of tachycardia, weight loss or heat intolerance.
Physical Examination

- Height 5' 10"
- Weight 175 lbs
- BP 120/70  Pulse 65/min regular
- Thyroid normal size with an enlarged left lobe.
  No discrete nodule. No adenopathy
- Heart regular rate and rhythm
- GI - no organomegaly
- Skin normal
- No myopathy, no tremor

A thyroid u/s revealed a well-circumscribed left thyroid nodule

Given the constellation of history, physical exam and radiographic findings the next step should be?

1. Thyroxine suppression
2. Fine needle aspiration
3. Measure TSH
4. Refer for surgery
5. Continued observation
THYROID NODULES-DIAGNOSIS

Palpated nodule
or
Incidentaloma (>1.0 cm)

Low TSH

Thyroid Scan

Hot

Observe

THYROID NODULES-DIAGNOSIS

TSH < 0.45 mIU/ml — Thyroid scan

MOLECULAR DEFECT
TSH RECEPTOR
ACTIVATING MUTATIONS

THYROID NODULES-DIAGNOSIS

Why Not a Thyroid Scan as a First Test?

1. Most nodules are cold and few cold nodules are malignant.
2. Helpful in stratifying multiple nodules.
3. Essential when the TSH is suppressed.
The TSH returns at 0.7 mIU/ml

The next step should be:
1. I\(^{131}\) scan
2. FNA under ultrasound
3. Surgical Removal
4. Radioiodine ablation
5. Serum thyroglobulin

THYROID NODULES-DIAGNOSIS

Palpated nodule
or
Incidentaloma (>1.0-1.5 cm)

Low
Thyroid Scan
Cold
FNA (benign, suspicious, cancer, indeterminate)

Hot
Observe
Remove

Normal-High
Ultrasound

THYROID NODULES-DIAGNOSIS

Fine Needle Aspiration: allows for stratification of nodules. 85% of the time a diagnosis can be made.

A. Benign - colloid goiter, macrofollicular adenoma
B. Suspicious - 50% chance of papillary carcinoma
C. Malignant - positive for malignancy-usually papillary carcinoma.
D. Follicular Neoplasm or Suspicious for follicular neoplasm
E. non-diagnostic
F. Atypia or follicular lesion of undetermined significance
THYROID ULTRASOUND GUIDED FNA

THYROID NODULES-DIAGNOSIS

Macrophages

Colloid

THYROID NODULES-DIAGNOSIS

Papillary Cancer

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The FNA returns showing a microfollicular lesion and is classified as indeterminate.

This result suggests:
1. A benign lesion with no further action required.
2. A 20% risk of malignancy, usually follicular cancer.
3. Could be consistent with a functioning adenoma
4. A high risk of medullary cancer
5. 2 and 3
6. 1 and 3

Appropriate management at this point would not include:
1. I^{123} scan
2. Removal of the nodule
3. Close f/up with a repeat u/s in 6 months
4. Ethanol ablation
5. Assessment of risk by Gene Expression Classifier (GEC-Affirma)

Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology

3,789 patients – 4,812 nodules
49 sites (70% community)
577 cytologically indeterminate nodules (n=265)

High sensitivity
And
Neg Pred Value

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THYROID NODULES-INDETERMINATE CYTOLOGY

Thyroid Scan

Because the TSH is not fully suppressed the nodule may not be fully autonomous or TSH independent. To confirm this the patient received L-thyroxine for 3 weeks, TSH < 0.05

Repeat scan - Suppression scan

Diagnosis: Hot Nodule

A 25 year old woman with hypothyroidism

A 25 yr old woman with a 5 year history of hypothyroidism treated with a stable dose of L-T4 presents (0.1 mg) presents with new amenorrhea for 3 weeks and is concerned about pregnancy and her thyroid hormone dose. She has never been pregnant previously and d/ced OCPs 12 months ago.

An appropriate next step would include all of the following except?

1. Measure TSH, hCG
2. Increase L-T4 to 0.125 mg and measure TSH, hCG
3. Measure anti-TPO abs and hCG
4. Measure TSH, FT4 and hCG
The hCG returns very positive with a TSH of 9.6 mIU/ml and a FT4 of 0.9 ng/ml.

The demand for T4 changes during pregnancy because?
1. Increased levels of thyroxine binding globulin (TBG).
2. Increased placental clearance.
3. Increased demand due to the fetus.
4. Increased peripheral metabolism by the liver.
5. 1, 2 and 3

In women with normal thyroid function, the demand for increased T4 is met by?
1. Inflammatory mediated T4 release.
2. The TSH-like activity of hCG.
4. Stimulation of the thyroid by human placental lactogen.
5. Enhanced TSH production by the pituitary.
PREGNANCY AND THE THYROID

Maternal Thyroid

Maternal Fertility Maintenance

T4/T3

Fetal Neurologic Function Growth

THYROID FUNCTION IN PREGNANCY

Burrow G NEJM

week 10 20 30 40

TSH hCG

GESTATIONAL THYROTOXICOSIS

TSH hCG

Clinical Findings
Nausea
Vomiting
Thyrotoxicosis
Remits

hyperemesis

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THYROID FUNCTION IN PREGNANCY

- TSH levels fall in the first trimester - 13% of women may have suppressed levels.
- Thyroid hormone levels rise in the first trimester and then level off. FT₄ can be low in the 3rd trimester.

_Trimester specific reference ranges are required._

Based on the thyroid function results the LT4 dose should be....?

1. Increased by 100%, because there may be a risk to the developing fetus.
2. Not changed because thyroid function will normalize later in pregnancy.
3. Increased by up to 25% given the history of autoimmune thyroid disease.
4. Not changed because pregnancy is associated with resistance to thyroid hormone.

HYPOTHYROIDISM IN PREGNANCY

<table>
<thead>
<tr>
<th>Haddow et al screened 25,000 women: weeks 14-18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T4/T3</strong></td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td>PLACENTA</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>HYPOTHYROID</th>
<th>CONTROL</th>
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</thead>
<tbody>
<tr>
<td>TSH</td>
<td>13.2</td>
<td>1.4</td>
</tr>
<tr>
<td>FT₄</td>
<td>0.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Abs</td>
<td>77%</td>
<td>14%</td>
</tr>
<tr>
<td>IQ (Rx)</td>
<td>111</td>
<td>107</td>
</tr>
<tr>
<td>IQ (-Rx)</td>
<td>100</td>
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### HYPOTHYROIDISM IN PREGNANCY

**Thyroid Hormone Replacement:**

- Increased TBG
- Increased demand
- Placental Clearance

<table>
<thead>
<tr>
<th></th>
<th>Hashimotos Before</th>
<th>Hashimotos During</th>
<th>Post-RAI Before</th>
<th>Post-RAI During</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 dose (ug/kg)</td>
<td>111</td>
<td>139</td>
<td>114</td>
<td>166</td>
</tr>
<tr>
<td>TSH</td>
<td>1.7</td>
<td>1.9</td>
<td>1.8</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Visit the BIDMC Thyroid Center

At [www.bidmc.harvard.edu/thyroidcenter/](http://www.bidmc.harvard.edu/thyroidcenter/)

HMS CME

**Thyroid Nodules**