Hyperthyroidism

Update on Diagnosis and Treatment

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Semantics

- Thyrotoxicosis
  - All clinical syndromes of excess thyroid hormone

- Hyperthyroidism
  - Excess production of thyroid hormones

Case 1

- 45 year old
  - Heat intolerance
  - Weight loss
  - Palpitations
  - Tremor
  - Increased frequency of bowel movements
  - Anxiety
  - Insomnia
  - Dyspnea
What is the most common cause of hyperthyroidism in the United States?

A. Graves Disease
B. Toxic Nodule
C. Toxic Multinodular Goiter
D. Thyroiditis

Hyperthyroidism

- Prevalence ~1%
- More common in women (~5x)
- Most common causes
  - Graves' disease
  - Autonomous nodule/s

Laboratory Diagnosis

- TSH
- T4
- T3
## Causes of Hyperthyroidism

<table>
<thead>
<tr>
<th>High Radioiodine Uptake</th>
<th>Low Radioiodine Uptake</th>
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<td>Graves’ Disease</td>
<td>Thyroiditis</td>
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<td>Autonomic (toxic) nodule/s</td>
<td>Thyroglobulin</td>
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<td>Trophoblastic disease</td>
<td>Exogenous thyroid hormone</td>
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<td>Pituitary tumor</td>
<td>Ectopic thyroid</td>
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<tr>
<td>TSH producing</td>
<td>Struma Ovari</td>
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<td>Metastatic Follicular Cancer</td>
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## Medications Causing Hyperthyroidism

1. Iodine induced hyperthyroidism
   - Iodinated contrast, kelp tablets
   - Amiodarone (type 1)
2. Destructive thyroiditis
   - Amiodarone (type 2)
   - Tyrosine kinase inhibitors (Sunitinib)
3. Alter thyroid autoimmunity (Graves’/thyroiditis)
   - Ipilimumab (immune adverse events)
   - Interferon alpha
   - Interleukin 2

## Case 1

- 45 year old woman
  - Heat intolerance
  - Weight loss
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  - Anxiety
  - Insomnia
  - Dyspnea
Graves’ Disease

- Autoimmune disorder
- Thyrotropin receptor antibodies (TRAb) stimulate the TSH receptor, increasing thyroid hormone production.

All of the following physical findings are characteristic of Graves’ disease except:

1. Exophthalmos
2. Thyroid nodules
3. Clubbing of the fingers
4. New periosteal bone formation in the hands and feet.

Physical Findings

- Diffuse goiter
- Ophthalmopathy – association with smoking
- Dermopathy
- Nail Changes
- Acropachy
Graves' Disease: Proptosis and Periorbital Edema

Dysconjugate Gaze

Graves' Disease: Onycholysis
Graves’ Disease:
Pretibial Myxedema

Dermopathy

Thyroid Acropachy

- Derived from Greek roots
  - akros - extremities
  - pachy - thick
- First described in 1933
- Soft tissue swelling and thickening of skin on hands and feet
- Clubbing
- New periosteal bone formation
  - Metacarpals
  - Metatarsals
  - Phalanges
Acropachy

Thyroid Acropachy
Acropachy

Treatment Options for Graves' Disease

- Medication
  - Methimazole (Carbimazole – "pro-drug")
  - Propylthiouracil (PTU)
  - Beta blockers
- Radioactive iodine ablation
- Surgery

What is the best treatment for Graves Hyperthyroidism?

1. Antithyroid medication
2. 131-I
3. Thyroidectomy
International Variation in the Treatment of Graves' Hyperthyroidism

A 2011 Survey of Clinical Practice Patterns in the Management of Graves' Disease

Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the ATA and AACE

Recommendation #4

“Patients with overt Graves’ hyperthyroidism should be treated with any of the following modalities: 131-I therapy, antithyroid medication or thyroidectomy.”

1/++0

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Hyperthyroidism

Treatment of Graves’ Hyperthyroidism

- All 3 treatment options are effective and relatively safe.
- The long term quality of life following treatment of Graves’ disease was found to be the same in patients allocated to one of the 3 treatment options.
- The final decision should incorporate the personal values and preferences of the patient.

Thyroid June 2011 v 21:593-646

A 2011 Survey of Clinical Practice Patterns in the Management of Graves’ Disease

Methimazole and Propylthiouracil (PTU) are equally safe and efficacious for the treatment of hyperthyroidism.

A. True
B. False


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Antithyroid Drugs: PTU and MMI

- Interfere with iodination of tyrosine residues to form thyroid hormones
  - PTU also interferes with conversion of T4 to T3
- Generally well tolerated
- Toxicity
  - Rash ~ 5%
  - Joint symptoms ~2%
  - Agranulocytosis < 0.5%

Antithyroid Drugs

- Methimazole
  - Longer half life
  - More potent
  - (Rarely ~ 0.03%) Associated with fetal malformations - "embryopathy" after first trimester exposure
    - Aplasia cutis – absent area of skin, usually a solitary defect on the scalp.
    - Choanal atresia - bony or membranous occlusion blocks the passageway between the nose and pharynx.
    - Omphalocele - protrusion of the intestine and omentum through a defect in the abdominal wall near the navel.
- PTU
  - Not associated with fetal malformations
  - Potential for severe hepatotoxicity (rarely ~ 0.01%)

PTU Hepatotoxicity: Rare but Severe

- 33 published reports of severe PTU-related liver failure in adults.
  - Incidence ~1/10,000 adults
  - 1-2 adults per year in US
- 14 cases in children
  - Incidence ~1/1000 children
  - 1 child per year in US
- Liver transplants related to PTU
  - 16 Adults
  - 7 children

Cooper DS, Rivkees, SA JCEM June 2009 94(6):18881-2
PTU Hepatotoxicity

- [Updated 04/21/2010] FDA has added a Boxed Warning to the label for propylthiouracil, to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication.
  
  Guideline Rec #12 "Methimazole should be used in virtually every patient who chooses antithyroid drug therapy, except during the first trimester of pregnancy when PTU is preferred." 1/++0

Pregnancy and Graves' Disease

Prevalence ~ 0.5%
Nodular Goiter

Pemberton's Sign
Facial plethora, distension of neck veins, stridor due to narrowing of the thoracic inlet from mediastinal extension of goiter.


Autonomous Nodule/s
- Thyroid nodules enlarge over time and can develop autonomy.
- Autonomous hormone production can be caused by somatic activating mutations of genes regulating thyroid hormone synthesis.
- Hormone production may progress from subclinical to overt hyperthyroidism, and the administration of pharmacologic amounts of iodine to such patients may result in iodine-induced hyperthyroidism.
- The prevalence of toxic nodular goiter increases with age.
Subclinical Hyperthyroidism: Definition

- Persistently low or undetectable serum TSH
- Normal free thyroxine (T4)
  - Direct measurement
  - Calculated using total T4 and TBG
- Normal triiodothyronine (T3)

Most patients with subclinical hyperthyroidism will progress to overt hyperthyroidism over the next five years.

A. True
B. False

TEARS (Thyroid Epidemiology, Audit and Research Study)

- Retrospective
- 2024 cases of subclinical hyperthyroidism in Tayside, Scotland
- Prevalence of 0.63%
- Patients who developed hyperthyroidism in the first year were excluded.
  - TSH 0.1-0.4 (4.7%)
  - TSH < 0.1 (10.2%)
- Patients who were not treated were evaluated at 2, 5, 7 years
  - TSH 0.1-0.4 (75%)
  - TSH <0.1 (21%)


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TEARS

- Very few patients developed overt hyperthyroidism
  - TSH < 0.1 ~ 2%
  - TSH 0.1 - 0.4 < 1%
- Most (~2/3) remained with subclinical disease
- Approximately 1/3 reverted to euthyroid
- Percentage of cases reverting to euthyroid increased over time

Subclinical Hyperthyroidism

Adapted from JCEM published ahead of print 10/6/2010 as doi: 10.1210/jc2010-0854

Subclinical Hyperthyroidism: Concerns

- Progression to overt hyperthyroidism
- Heart
  - Atrial fibrillation (~ 3 x increase)
  - Congestive heart failure
  - CHD events and mortality
- Bone
  - Osteoporosis
- Cognition
  - Dementia
Subclinical Hyperthyroidism: Mortality

Analysis of 10 Prospective Cohort Studies

Conclusion:
Endogenous subclinical hyperthyroidism is associated with increased risks of total CHD mortality, and incident atrial fibrillation with the highest risks of CHD mortality and atrial fibrillation when TSH is less than 0.1 mIU/L.

### Treatment of subclinical hyperthyroidism

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<td>A. True</td>
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<td>B. False</td>
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Hyperthyroidism has been shown to decrease the risk of atrial fibrillation and congestive heart failure.

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### Who Should be Treated?

- TSH persistently < 0.1
- Older patients (>65 years old)
- Cardiac disease
- Osteoporosis
- Symptomatic

| Rec 65 2/+00 | TSH <0.1 |
| Rec 66 2/+00 | TSH suppressed but > 0.1 |

Guidelines: "We suggest that patients should be treated with either 131-I or thyroidectomy. On occasion, long term, low dose treatment with methimazole may be appropriate. 2/+00"
Atypical Clinical Presentations of Hyperthyroidism

- Weight loss/anorexia
- Weakness
- Atrial arrhythmias
- Thyroid not palpable

Case 2:

- 23 year old man with no previous medical history presented to the ER with bilateral paralysis of lower extremities
- Up late studying for exams and eating Twizzlers and other "junk food"
- Woke up at 5 am unable to move his legs
- Called ambulance at 9 am
- K 1.5 in the ED
- Noted to have a goiter on exam
- Labs confirmed hyperthyroidism
Thyrotoxic Periodic Paralysis

- **Incidence**
  - 2-20% in Asian thyrotoxic population
  - 0.1% in North American thyrotoxic patients
  - Ratio Men:Women 17:70:1
  - Associated with any form of thyrotoxicosis, even exogenous

- **Symptoms**
  - Prodrome symptoms: muscle aches, cramps, stiffness
  - Proximal > Distal Muscles
  - Lower limbs > Upper limbs
  - Total paralysis of respiratory, bulbar, ocular muscles have been reported in severe cases
  - Attacks can last up to 72 hours with complete resolution between episodes

Biochemical abnormalities

- **Hypokalemia**
- **Hypophosphatemia**
- **Hypomagnesemia**
- **Elevated CPK in 2/3 of patients**

Electrolyte abnormalities are due to massive shifts into cells rather than net body loss.

Thyrotoxic Periodic Paralysis

- **Pathogenesis**
  - Increased Na-K-ATPase pump activity, stimulated by thyroid hormone, catecholamines, insulin
  - Increased number of pumps, reversible when euthyroid

- **Treatment**
  - Supplementation with KCL
  - Nonselective beta-blocker
  - Avoid precipitants (heavy carbohydrate meals)
  - Definitive treatment for hyperthyroidism
Pitfalls in the Diagnosis of Hyperthyroidism

How the TSH can lead you astray......

Medications

- Suppress TSH
  - Dopamine/Dobutamine
  - High dose glucocorticoids
  - Opiates
- Increase Free T4
  - Heparin
  - Furosemide
  - Salicylates/Salsalate/Diclofenac

Hypothalamic Pituitary Thyroid Axis
Don’t rely on TSH to assess thyroid function in the setting of pituitary disease!
Check T4 instead.

Case 1

- 45 year old woman
  - Heat intolerance
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  - Insomnia
  - Dyspnea

Graves Disease

- The patient was diagnosed with Graves’ disease and hyperthyroidism 3 months ago.
- Initial labs: Free T4 3.3, TSH < 0.02
- Six weeks ago she was treated with radioactive iodine.
- Repeat TSH < 0.02
Is She Still Hyperthyroid?

A. Yes  
B. No  
C. Need more lab tests

Is the low TSH an accurate reflection of her current thyroid status?

TSH and FT4 after Treatment of Hyperthyroidism
More Labs

- TSH < 0.02
- Free T4 1.2 (0.92 – 1.7 ng/dl)
- Diagnosis: Euthyroid

Don’t use TSH alone to assess thyroid function in the setting of recent hyperthyroidism!

End