Endocrinology

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Outline

- Diabetes Mellitus
- Pituitary gland
- Thyroid gland
- Adrenal gland
- Calcium and bone metabolism
- Male Hypogonadism
- Gynecomastia
- Hirsutism
- Genetic Syndromes

Areas tested most heavily

- Diabetes mellitus
- Thyroid disorders
- Disorders of calcium metabolism and bone
- Lipid disorders (covered under Cardiology)
- Adrenal disorders
- “Disorders of testes/male reproduction”
- Pituitary, water metabolism, endocrine tumors, endocrine syndromes, polyglandular disorders, endocrine hypertension
General Principles

- Majority of endocrine disorders due to too little or too much of a normally occurring hormone
- Make a biochemical diagnosis before proceeding with imaging

Criteria for Dx of DM

Presence of any of the following:

1. Symptom of DM + a random glu ≥ 200 mg/dL
2. Fasting glu ≥ 126 mg/dL
3. 2-hour postprandial glu ≥ 200 mg/dL during oral glucose tolerance test with 75 g glucose load
4. A1C ≥ 6.5%

DM Risks and Complications

- Microvascular:
  - Retinopathy
  - Nephropathy - heralded by microalbuminuria
  - Neuropathy
  → Glycemic control (DCCT, UKPDS)
- Macrovascular:
  - Atherosclerosis/CV Disease
- Risk factor management
  - BP<130/80 mm Hg
  - Lipids: LDL at least ≤100 mg/dL (optional ≤70 mg/dL)
  - Tobacco cessation
  - Aspirin for 2nd prevention
**CASE 1**

67 yo obese man (BMI 34) has had DM2 for 8 yrs. Originally treated successfully with diet, over time his HBA1c increased to 8.1%, and improved again to 6.6% with the addition of metformin 1 g bid. He continues to exercise and follow dietary recommendations, but his HbA1c is now 7.7%.

What is the most appropriate add’l intervention now?

a. Add repaglinide therapy before bkfst and dinner  
b. Increase metformin to 850 mg tid  
c. D/c metformin and begin glipizide  
d. Add glipizide to the metformin

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**CASE 2**

A 64 year old woman with DM presents with worsening glycemic control. Fasting glucose values are constantly above 200. She is on metformin and sulfonylurea.

What is the most appropriate next therapy for this patient?

a. Start morning basal insulin (e.g. glargine or NPH) and discontinue all oral agents  
b. Start morning basal insulin, maintain sulfonylurea and discontinue metformin  
c. Start morning basal insulin, maintain metformin and discontinue sulfonylurea.  
d. Start bedtime basal insulin, maintain oral agents
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Therapy in DM2 - Lifestyle

- Lifestyle modification:
  - Exercise
  - Weight reduction
    - Including bariatric surgery (DM remission)
  - Dietary change
- Improve glycemic control
- Prevent progression of disease

Therapy in DM2 - Meds

- Stepwise approach – recs:
  - Metformin first
    - Initiate at dx
    - Contraindications – CKD, liver dz
      - Risk of lactic acidosis
  - Add sulfonylurea
  - Basal insulin (e.g. glargine, NPH, le vemir)
CASE 3
You are asked to see a 72 year old man with a history of CHF and previously well controlled DM2, but now a HbA1c of 8.2%. He is on Glyburide and Metformin at max doses.

What is the most appropriate change to his regimen?

a. Add rosiglitazone
b. Add pioglitazone
c. Add bedtime insulin (NPH or glargine)
d. Add acarbose

Therapy in DM2 – Tier 2
- Lifestyle Modification + Metformin
- Thiazolidinediones
  - Rosiglitazone is currently not recommended (b/c of suggestions of increased heart dz – controversial)
  - Pioglitazone – TZD of choice
    - If no hx CHF
    - No risk of frx (e.g. postmenopausal women)
- GLP-1 agonist rx – insuff safety info
- Add basal insulin
Case 4

58 yo post-menopausal woman with DM2 on metformin and glipizide for 4 yrs. She has continued to gain weight since her dx (BMI 34 to 38). She is very scared of hypoglycemia. HbA1C 8%.

What medication would you add next?

a. Bedtime basal insulin
b. Sitagliptin
c. Pioglitazone
d. Exenatide

Exenatide

- GLP-1 Agonist
- SQ injection BID – fixed dose
- Wt. loss
- Nausea, some vomiting, diarrhea
- No hypoglycemia
- A1C drop ~0.5-1%
- Expensive
- Limited long term data
- Acute pancreatitis (necrotizing)
Amylin & GLP-1 Therapies

- Amylin and GLP-1 (Glucagon like peptide) are relatively or absolutely deficient in diabetes
- Broken down by Dipeptidyl peptidase IV (DPP-IV)
- Increasing their levels in diabetics restores normal homeostasis, namely:
  • Slow gastric emptying
  • Decrease post-prandial glucagon
  • Decrease appetite
  ➢ Lower HbA1C and cause weight loss

Case 5

72 yo man previously well controlled DM2 on metformin (HbA1C 6.2%), recently developed CKD with Cr in 1.5-1.7 mg/dl range. Metformin has been stopped. What should be started instead?

a. Sitagliptin
b. Bedtime insulin glargine
c. Pioglitazone
**Sitagliptin**

- DPP IV inhibitor
- Limited A1C reduction (~0.5-0.8%)
- Can be renal dose adjusted
  - CKD pts
  - DM2 in fairly good control
- Weight neutral
- Expensive

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**Amylin & GLP-1 Therapies**

<table>
<thead>
<tr>
<th>Class</th>
<th>Names</th>
<th>Dosing</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Amylin Analogs</td>
<td>Pramlintide</td>
<td>SQ TID</td>
<td>Only for pts on insulin</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Exenatide</td>
<td>SQ BID</td>
<td>Promotes wt loss; DM2 pts only. Not if on insulin</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>SQ QD</td>
<td></td>
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<tr>
<td>(DPP-IV) Inhibitors</td>
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**CASE 6**

You are asked to see a 65 year old woman with rheumatoid arthritis who was diagnosed with DM one month ago. She has been on prednisone for the past 4 months. She is not monitoring her BG values.

**Labs:** Fasting BG =105. HbA1c = 8.0 %.

You decide to start her on insulin.

What is the most appropriate insulin regimen for this patient?

- a. NPH twice daily
- b. Glargine or NPH at bedtime
- c. Short acting insulin before meals and bedtime
  - NPH or Glargine
- d. Short acting insulin before meals
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   d. Short acting insulin before meals

CASE 7
You see a 37 yo man because of a random glucose of 165 mg/dL. One year prior, he was diagnosed with schizophrenia and started on olanzapine. He has gained 12 lbs in the last year, but is otherwise doing well. He has a +FHx of DM2. BMI is 27, remainder of exam is normal.

**Labs:** FBGlu: 120, 118 mg/dl. N/l lytes, LFT’s. Tot Chol: 230 mg/dl.
You recommend lifestyle modifications and: What is the most appropriate change to his regimen?

a. Add glipizide  
   b. Discontinue olanzapine  
   c. Substitute risperidone for olanzapine  
   d. Substitute ziprasidone for olanzapine

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A 50 year old man is unable to work because of lethargy. A year before, he was in a car accident and sustained a head injury. He was pursuing an insurance claim and attributed his symptoms to anxiety. His libido has been low since the car accident.

Examination: sparse eyebrows, axillary and pubic hair; delayed relaxation of biceps and ankle jerks.

Investigations

Hemoglobin: 13 (13.6-17.5); Na: 131, K: 3.8; Free T4: 7 (9-24), TSH: 0.4 (0.5-5.0)

What is the appropriate next step?

a. Start methimazole 30 mg qd
b. Check thyroid auto antibodies
c. Perform a cosyntropin stimulation test
d. Obtain a radioactive iodine uptake and scan

**Hypopituitarism**

- Primary organ failure more common
- BUT consider hypopituitarism in cases of hypothyroidism, hypoadrenalism and hypogonadism
- Lose, in this order: GH, gonadotrophins, TSH, ACTH, Prolactin
- ADH deficiency only if posterior pituitary involved
**Case 9**

A 24 year old woman presents complaining of worsening fatigue 6 months after delivering twins. Screening for postpartum hypothyroidism revealed a TSH of 1.7 mU/ml (0.5-5.0). What do you recommend next?

a. Help at home to look after the twins  
b. Measure Free T4  
c. Perform a cosyntropin stimulation test  
d. Measure a prolactin level

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**Post-partum 2\text{ary} Hypothyroidism**

- Primary end organ failure is more common
  - Check FT4 to confirm
  - Then cosyntropin stimulation test and prolactin
- Sheehan’s
  - Pituitary infarction due to hypotension in setting of severe post-partum hemorrhage
  - “Empty sella” on MRI
- Lymphocytic Hypophysitis
  - Autoimmune lymphocytic infiltration of pituitary
  - Diffusely enlarged pituitary gland on MRI
  - Isolated TSH and ACTH deficiency
  - Patients almost always peri-partum women
Hypopituitarism: Dx and Tx

- In general, treat underlying cause
- Central hypogonadism
  - Low FSH; rule out hyperprolactinemia before making diagnosis
  - Tx: Men: testosterone replacement;
    Women: if premenopausal, OCP's;
    postmenopausal: consider low dose estrogen
- Central hypothyroidism
  - TSH is not reliable for screening or for monitoring
  - Diagnosis depends on low Free T4
  - Tx: LT4 therapy, but do not start until adrenal insufficiency has been ruled out

Hypopituitarism: Dx and Tx cont’d

- Central adrenal insufficiency
  - Normokalemia (b/c aldosterone secretion intact)
  - Hyponatremia
  - Dx: cosyntropin stimulation test
    - Random cortisol or ACTH level not useful
  - Tx: hydrocortisone
- Prolactin deficiency
  - Inability to lactate
  - No treatment

Case 10

A 32 yr old woman presents to her gynecologist with a 6 month history of fatigue, some weight gain and amenorrhea. Exam reveals dry skin, coarse hair and delayed DTR relaxation.

Investigations
Prolactin 58 ng/ml (<20);
Pituitary MRI – enlarged pituitary gland without any obvious adenoma

What is the appropriate next step?

- a. Repeat the prolactin in 3 months
- b. Refer to neurosurgery
- c. Initiate treatment with bromocriptine or cabergoline
- d. Check TSH and Free T4
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**Hyperprolactinemia**

- **Physiologic:**
  - Pregnancy
  - Prolactin up to 200 ng/ml in 2nd trimester
  - Lactation or any nipple stimulation

- **Pathologic:**
  - Pituitary tumors – mostly microadenomas
  - Pituitary stalk lesions
  - Hypothyroidism
  - Chronic kidney disease
  - Hypothalamic lesions

- **Pharmacologic:**
  - Estrogen
  - Psychiatric meds (antipsychotic DA antagonists, SSRIs, TCAs)
  - H2 blockers (ranitidine, cimetidine)

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**Hyperprolactinemia: Syx/exam**

- **Galactorrhea**
- **Hypogonadism:**
  - **Women:** amenorrhea or oligomenorrhea with anovulation and infertility in 90%, hirsutism
  - **Men:** impotence, decreased libido
- **If pituitary adenoma, local tumor extension symptoms**
  - headache, visual field cuts, hypopituitarism
Prolactinoma

- **Diagnosis:**
  - Elevated prolactin:
    - PRL >200 ng/ml virtually diagnostic of prolactinoma
    - PRL 100-200 ng/ml usually prolactinoma
    - PRL 20-100 ng/ml may be microadenoma but exclude other causes
  - Normal TFT’s and negative pregnancy test
  - MRI of pituitary
- **Treatment:** medical 1st line
  - Dopamine agonists (bromocriptine, cabergoline)
    - DA inhibits prolactin secretion

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CASE 11

With respect to acromegaly which of the following statements is false.

a. The majority of acromegaly inducing adenomas are smaller than 1 cm
b. Hyperprolactinemia leading to hypogonadism may co-exist
c. Hypogonadism due to gonadotrophin deficiency may occur
d. Failure of growth hormone suppression during a glucose tolerance test is a valuable diagnostic test
e. There is a recognized association with Carpal Tunnel Syndrome
Pituitary Tumors: GH Tumors

- 80% are macroadenomas
- 15% co-secrete prolactin
- Very rarely (<1% cases), acromegaly is due to ectopic GH or GHRH production
  - Lung CA, carcinoid, or pancreatic islet cell tumors

Clinical features due to excess IGF-I and mass effect of the tumor
- Hypertension
- Glucose intolerance or DM
- Increased colonic polyp frequency
- Carpal Tunnel Syndrome
- Hypogonadism
- Visual field cuts and h/a’s

Soft tissue proliferation:
- Coarsening of facial features
- Hand and foot enlargement
- Sweaty palms and soles
Pituitary Tumors: GH Tumors

- **Diagnosis:**
  - Elevated IGF-1 is the hallmark
  - Dx: oral glucose tolerance test
  - Random GH level not helpful!
- **Therapy:**
  - Surgery
  - Medical if surgery not curative
    - Somatostatin analogues (octreotide)
      - Somatostatin inhibits GH production
    - GH Recept antagonists (pegvisomant)

Pituitary tumors

- Microadenomas are < 1cm
- Macroadenomas are >1cm
- Types of tumors
  - 60% prolactinomas
  - 20% GH producing
  - 10% ACTH producing
  - 10% non-functioning
  - Rare: TSH, LH/FSH or α-subunit producing

Pituitary tumors - Presentation

- **Symptoms/Exam:**
  - Neurological sx
    - headaches
    - visual field cuts
    - nerve palsies
  - Hormonal excess or deficiency
  - Incidental discovery on imaging study
    - up to 10% general population have pituitary incidentalomas
Pituitary tumors - Evaluation

- Once tumor is identified, must determine if functional or causing hormonal deficiency:
  - TSH, FT4
  - Prolactin
  - ACTH, cortisol
    - Cosyntropin stimulation test if suspect deficiency
    - 24 hr urinary cortisol or dexamethasone suppression test if suspect excess
  - LH/FSH + testosterone in men
  - IGF-I

Pituitary tumors - Treatment

- Surgery: transsphenoidal approach is successful in ~90% of patients with microadenomas
- Medical:
  - Prolactinomas
  - GH producing tumors
- Radiotherapy after surgery and/or medical therapy fails or poor surgical candidates:
  - Conventional XRT or
  - Gamma knife

CASE 12

A middle aged woman is referred with thirst, polydipsia and polyuria. She was in a car accident 9 months previously and her symptoms started soon after this.

Examination is normal - BP 120/80 without postural changes. Her 24 hr urine volumes range from 7 to 12 liters.

Investigations
Na: 130 K: 3.5, BUN: 2, glucose: 100, plasma osmolality: 268 mOsm/kg (285-293);
Urine: osmolality 50 mOsm/kg (300-900 mOsm/kg), no glucose

What is the appropriate next step?

a. MRI of the pituitary gland
b. 10 mg DDAVP treatment once or twice a day
c. Water restriction to 2-3 liters/day
d. Thiazide diuretic
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Diabetes Insipidus (DI)

- Hallmarks
  - ↓ ADH concentration or action
  - Dilute urine (SG <1.005, osmolality <200)
  - Elevated serum osmolality
  - Eunatremia if free access to water
  - Hypernatremia otherwise

Diabetes Insipidus – cont’d

- **Central DI** – deficient secretion of ADH by the pituitary gland
- **Nephrogenic DI** – resistance to ADH actions
- **Primary polydipsia** (Psychogenic Polydipsia)
Diagnosing etiology of polyuria

<table>
<thead>
<tr>
<th>Test</th>
<th>Central DI</th>
<th>Nephrogenic DI</th>
<th>Primary Polydipsia</th>
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<tr>
<td>Random plasma osmolality</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Random urine osmolality</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Urine osmolality during water deprivation</td>
<td>No Change</td>
<td>No Change</td>
<td>↑</td>
</tr>
<tr>
<td>Urine osmolality after IV DDAVP</td>
<td>↑</td>
<td>No Change</td>
<td>↑</td>
</tr>
<tr>
<td>Plasma ADH</td>
<td>↓</td>
<td>Normal to ↑</td>
<td>↓</td>
</tr>
</tbody>
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Treatment

- **Central DI** – DDAVP (intranasal, IV, SC, PO)
- **Nephrogenic DI** – treat underlying disorder if possible.
  - Thiazide diuretics and amiloride can be helpful
  - Low Salt Diet
- **Primary polydipsia** – limit water intake

**CASE 13**

36 yo woman presents complaining of fatigue, 5 lbs weight gain, irregular menses, constipation and dry skin over the last 6 months.

You want to evaluate her thyroid, what would you order:

a. Radioactive iodine uptake and scan
c. TSH, FT4, thyroglobulin
d. TPO antibodies
e. TSH, FT4
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Thyroid Tests
- Thyroid Function Tests (TFTs):
  - TSH – good to screen initially
  - Free T4 – needed to follow patients and to rule out central thyroid disease
  - Total or Free T3 – to r/o or r/i T3 thyrotoxicosis
- Thyroid antibodies
  - TPO and Tg Ab’s: sensitive for autoimmune thyroid dz, esp. Hashimoto’s
  - TSH rcptr stimulating immunoglobulins (TSI): specific for Graves’ disease

Hypothyroidism
- 2% of adult women
- Etiologies:
  - Hashimoto’s – most common
  - Drugs: amiodarone, lithium, interferon, iodide
  - Iatrogenic: post surgical, post RAI rx or post XRT for neck cancer
  - Rare causes: iodine deficiency, central hypothyroidism, peripheral resistance to thyroid hormone.
Hypothyroidism

- Symptoms are non specific:
  - Fatigue
  - Wt gain
  - Cold intolerance
  - Dry skin
  - Menstrual irregularities
  - Constipation
  - Periorbital edema, Bradycardia, hoarse voice, hair loss

- Diagnosis: ↑TSH and ↓FT4
- Treatment: LT4 replacement to normal TSH
  - 1.6 mcg/kg/d
  - If heart disease: start at 12.5-25 mcg/d and increase by 25 mcg q month

CASE 14

28 yo healthy woman presents to the ER complaining of 3 months of chest palpitations, 5 lbs weight loss despite increased appetite and hyperdefecation. Her exam is notable for HR of 103, but is otherwise normal.

Investigations:
CBC, electrolytes normal; TSH: <0.01 (0.5-4.7) FT4: 27 (9-24)

Your next step is:
  a. Discharge her with f/u visit in 1 week
  b. Initiate propranolol
  c. Start therapy with methimazole
  d. B and C
**Hyperthyroidism**

- Most often due to Graves’ disease
- DDx includes:
  - Solitary toxic nodule
  - Multinodular goiter
  - Thyroiditis
  - Rare: exogenous thyroid hormone ingestion, struma ovarii, hydatidiform mole
- Symptoms: weight loss, anxiety, fatigue, palpitations, hyperdefecation, heat intolerance, sweating, amenorrhea

**Hyperthyroidism Cont’d**

- Exam:
  - Lid lag
  - Tachycardia
  - Increased pulse pressure
  - Hyper-reflexia
- Diagnosis:
  - Low TSH, high FT4 &/or T3
  - May need RAIU/scan if etiology unclear

**Thyroid Uptake and Scan**

Radioactive iodine uptake and scanning helpful in evaluation of hyperthyroidism

<table>
<thead>
<tr>
<th>Decreased Uptake</th>
<th>Diffusely Increased Uptake</th>
<th>Uneven Uptake</th>
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<tbody>
<tr>
<td>Thyroiditis</td>
<td>Graves’ Dz</td>
<td>Multinodular goiter (hot and cold)</td>
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<tr>
<td>Exogenous hyperthyroidism</td>
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<td>Solitary Toxic nodule (hot)</td>
</tr>
<tr>
<td>Struma Ovarii</td>
<td></td>
<td>Cancer (cold)</td>
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</table>
Hyperthyroidism: Treatment

- **Medical:**
  - Methimazole (MMI) and Propylthiouracil (PTU) decrease thyroid hormone production.
  - **In pregnancy – PTU is first choice**
  - β-blockers to control tachycardia
- **Radioiodine (RAI):**
  - Tx of choice for toxic nodules
  - 90% cure rate for Graves’
- **Surgical:**
  - If uncontrolled disease in pregnancy
  - For extremely large goiter
  - If patient objects to RAI

Hyperthyroidism: Graves’

- **Females:** males = 5:1
- **Unique characteristics:** Exophthalmos due to infiltrative orbitopathy
  - I\textsubscript{131} Rx can worsen eye disease

CASE 15

39 yo woman with Graves’ disease presents to the ER with severe dyspnea, nausea, diarrhea and a feeling of impending doom. She had been on MMI for 7 months, but d/c’d it 9 mos ago b/c of rash with pruritus.

**Exam:** T 39.6C, HR 144; BP 106/48

Hyperkinetic, delirious, diaphoretic and dyspneic. Also noted are a large goiter and loud bruit over the thyroid.

While awaiting laboratory results, therapy could include each of the following EXCEPT:

a. PTU or MMI
b. Stable Iodine
c. Corticosteroids
d. Radioactive Iodine
e. β-blockers
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Thyroid Storm

- Marked hypermetabolic and adrenergic state
  - Fever (38-41C), flushing, sweating, delirium, tachycardia, heart failure, agitation, nausea, vomiting, diarrhea, jaundice, coma
- Treat with propranolol, PTU, hydrocortisone, and stable iodide (sodium ipodate or potassium iodide)

CASE 16

A 42 year old man presents with weight loss, palpitations and a sore neck. He had a viral illness about 2 weeks ago. No PMH or FH of thyroid disease.

On exam: pulse: 104, T: 103F; extreme neck tenderness

Labs: TSH < 0.01 (0.5-4.7); FT4 16.8 pmol/L (9-24)

What is the best study to establish the diagnosis?

a. Measurement of serum TPO Ab
b. Measurement of serum thyroid stimulating immunoglobulin (TSI)
c. Needle aspiration and biopsy of the thyroid
d. Radioactive iodine ($^{123}$I) uptake and scan
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Subacute Thyroiditis

- Viral in etiology
- Exam: tender large thyroid, fever
- Labs:
  - High ESR;
  - negative Ab’s;
  - low RAI uptake
- Treat with NSAID’s + steroids if very severe
- Self-resolving

CASE 17

A 60 year old man with paroxysmal atrial fibrillation presents to the emergency room with 1 week of progressive fatigue and weakness. His medications include amiodarone.

Investigations

TSH: 0.03 (0.5-4.7), FT4: 33 (9-24), normal CBC and electrolytes. ECG: 110 sinus tachycardia.

You would recommend:

a. Thyroid uptake and scan with possible ablation
b. Start anticoagulation and prepare for cardioversion
c. A beta blocker, methimazole and prednisone
d. Discontinue amiodarone and start a beta blocker
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You would recommend:

a. Thyroid uptake and scan with possible ablation
b. Start anticoagulation and prepare for cardioversion
c. A beta blocker, methimazole and prednisone
d. Discontinue amiodarone and start a beta blocker

Amiodarone and hyperthyroidism

- Thyroiditis
  - Destructive process
  - Thyroid hormone dumping
  - Low flow on U/S with Doppler
  - Responds to prednisone

- Hyperthyroidism
  - Excess thyroid hormone (TH) production
  - Inability to shut off TH production in response to iodine load (Jod Basedow effect)
  - Often in pts with multinodular goiters
  - High flow on U/S with Doppler

Amiodarone Thyroiditis

- Amiodarone is 37.3% iodine; stored in fat, myocardium & liver
- 3 changes in thyroid f/n due to amiodarone:

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Tests</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Asymptomatic TFT 1. ↑FT4 &amp; Tot T4; ↑T3 &amp; ↑TSH</td>
<td>1. None – will normalize</td>
<td></td>
</tr>
<tr>
<td>2. Hypothyroidism 2. ↑TSH; ↑FT4 &amp; T3</td>
<td>2. As for hypothy</td>
<td></td>
</tr>
<tr>
<td>3. Hyperthyroidism 3. ↑TSH; ↑FT4 &amp; T3</td>
<td>3. MMI; β-blocker; +/- prednisone</td>
<td></td>
</tr>
</tbody>
</table>

- Cannot use RAI because of high body iodine
**CASE 18**

A 75 year old man is referred for a right thyroid nodule, he has normal thyroid function tests.

The next step is to

a. Place patient on L thyroxine suppressive treatment
b. Refer him to an endocrine surgeon
c. Obtain a fine needle aspiration biopsy
d. Arrange for a radionucleotide uptake scan

---

**Thyroid Nodules and Cancer**

- **Rule of 90% for thyroid nodules:**
  - 90% benign
  - 90% are cold on RAIU scan
    - 15-20% of these are malignant
  - 90% of thyroid malignancies present as nodules

- **Evaluation:**
  - Check TFT’s
  - **Biopsy with FNA** all euthyroid and hypothyroid palpable nodules
    - incidentally discovered nodules or nodules within a multinodular goiter if >1cm
Thyroid Cancer

- Papillary (75%): most common, spreads lymphatically. Excellent prognosis.
- Follicular (16%): more aggressive, spreads locally and hematogenously. Metastasizes to bone, lungs and brain.
- Medullary (5%): Tumor of parafollicular cells. May secrete calcitonin
  - 15% familial or associated with MEN 2A and MEN 2B.
- Anaplastic: poor prognosis.
- Other: metastases to thyroid (breast, kidney, melanoma, lung); lymphoma (1st or mets).

Thyroid Cancer Treatment

- All require surgical thyroidectomy first
- Papillary and follicular cancer are then followed by:
  - RAI ablation
  - LT4 rx to suppress TSH
  - Thyroglobulin is a good marker for the presence of thyroid cancer (after thyroidectomy)
    - Used to follow patients long term

CASE 19

75 yo man is in the ICU for UTI, complicated by sepsis. His T3 is 52 mcg/dl (70-132) and FT4 is 1.0 ng/dl (0.8-2). He improves over the following 5 days. Repeat TFT's:
- T3: 102 mcg/dl (70-132); FT4: 1.2 ng/dl (0.8-2); TSH: 22 mU/L (0.4-4.5).

Which of the following is the most likely explanation of these test results?

A. Subacute thyroiditis
B. Lymphocytic thyroiditis (Hashimoto’s)
C. Severe myxedema
D. Nonthyroidal illness
E. Hypothalamic infarction
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C. Severe myxedema
D. Nonthyroidal illness
E. Hypothalamic infarction

Low T3 most common abnormality

Euthyroid Sick Syndrome

- AKA Non-thyroidal illness
- Hospitalized or terminally ill patients
- Asymptomatic
- Most common abnormality:
  - LOW T3 LEVEL
- TSH levels vary
  - Low-normal acutely
  - Can be frankly elevated in recovery phase
- No need for thyroid medications

CASE 20

With respect to Addison’s disease which one of the following statements is false

a. Addison’s can occur in both autoimmune polyglandular syndrome type 1 and type 2
b. Bilateral adrenal hemorrhage is now a relatively common cause of adrenal insufficiency
c. A normal cortisol value excludes the diagnosis
d. Postural hypotension is often a feature
e. Moderate hypercalcemia is a feature of Addison’s disease
**CASE 20**

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---

**Adrenal Insufficiency: Etiologies**

- **Primary AI:**
  - Autoimmune
  - Gland destruction
    - Metastases, lymphoma
    - Hemorrhage
    - Infiltrative disorders: amyloid, hemochromatosis
    - Infections
  - Drugs: ketoconazole, etomidate
  - Rare: congenital adrenal hyperplasia, adrenal leukodystrophy

- **Secondary AI:**
  - Iatrogenic: glucocorticoids & anabolic steroids
  - Pituitary or hypothalamic tumors

---

**AI: Clinical Features**

- Vague sx:
  - Weakness
  - Fatigue
  - Anorexia
  - Weight loss
  - Nausea
  - Vomiting
  - Diarrhea
  - Unexplained abdominal pain
  - Postural lightheadedness
AI: Diagnosis

- Labs: ↓ Na⁺, ↑ K⁺, eosinophilia, mild metabolic acidosis, ↑ Ca²⁺
- **Step 1**: confirm diagnosis
  - Any random cortisol ≥ 18 µg/dl rules out AI
  - Cortrosyn stimulation test
    - Obtain baseline cortisol and ACTH
    - Inject Cortrosyn 250 µg IM or IV
    - Check cortisol level 45-60 minutes later
    - Normal if post stimulation cortisol ≥ 18 µg/dl
- **Step 2**: distinguish 1° from 2°
- **Step 3**: evaluate cause (CT abdomen or MRI pituitary)
AI: Treatment

- Hydrocortisone 10-30 mg/day
  - Stress doses:
    - Minor stress – double usual dose
    - Major stress: 50 mg IV q 6-8 hrs, and taper
- For 1° AI, also need:
  - Fludrocortisone 0.05-0.1 mg/day

Cushing’s Syndrome

- Exogenous steroids: #1 cause
- Endogenous:
  - Cushing’s disease (70%): ACTH from pituitary adenoma
  - Ectopic ACTH (15%)
    - Small cell lung CA most common
    - Bronchial carcinoids
- Adrenal (15%):
  - Adenoma
  - Carcinoma
  - Nodular adrenal hyperplasia

Common features of Cushing’s syndrome:

- Psychological
- Puffiness
- Moon face
- Osteoporosis
- Hypertension
- Central obesity
Cushing’s: Diagnosis - principles

- **Step 1**: confirm excess cortisol secretion
  - Overnight Dexamethasone Suppression Test
  - 24-hr Urine Free Cortisol
- **Step 2**: ACTH dependent or independent?
  - Check ACTH
- **Step 3**: localize the source (pituitary, adrenals, or ectopic) with imaging
- **Step 4**: ancillary testing if above are equivocal

Cushing’s: Treatment

- **Cushing’s disease**:
  - Transsphenoidal adenoma resection.
- **Ectopic ACTH**:
  - Treat underlying neoplasm.
  - If neoplasm is not identifiable or treatable:
    - Pharmacologic blockade of steroid synthesis (ketoconazole, metyrapone, aminoglutethimide).
    - Potassium replacement (± spironolactone)
    - Bilateral adrenalectomy if all else fails.
- **Adrenal tumors**:
  - Unilateral adrenalectomy.

CASE 21

A 35 year old lawyer had hypertension diagnosed 1 year ago. Despite treatment with β-blocker, calcium channel blocker and ACE inhibitor, his blood pressure remains elevated. On examination his BP is 210/110; Fundi – grade III retinopathy. No other past medical history of note. Rest of examination is normal.

**Investigations**

Na: 142, K: 3.5, Creatinine: 1.2

What is the next step?

a. Plasma renin activity and plasma aldosterone concentration
b. CT scan of the adrenals
c. 24 hr urine for VMA
d. Morning basal 17-hydroxyprogesterone level
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Primary Aldosteronism (PA)
- Accounts for 0.5-10% cases htn
- Results from autonomous aldosterone production, due to:

Primary Aldosteronism: Features
- Hypertension
- Hypokalemia
  - May be absent
  - Exacerbated by diuretics
- Paresthesias if severe hypokalemia
- Mild alkalosis on laboratories
Primary Aldosteronism: Dx

- Screening:
  - Must first replete potassium
  - Plasma aldosterone (PA) $>20-25$ $\rightarrow$ suggestive
    Plasma Renin Activity (PRA)
    - But PA must be high (>15 ng/dL)

- Confirmatory test:
  - Salt load: 1 g NaCl tid for 3 days
  - 24 hr urine aldosterone $>12$ mcg/24 hr with concomitant 24 hr urine Na $>200$ mmol/d

Primary Aldosteronism cont’d

- Diagnosis Cont’d: Imaging with CT
  - Unilateral lesion
  - Bilateral Hyperplasia, or no lesion seen:
    - Adrenal vein sampling – measure cortisol and aldosterone to lateralize source of aldosterone excess

- Management:
  - Unilateral lesion $\rightarrow$ resect
  - Bilateral hyperplasia or no lesion $\rightarrow$
    medical rx with spironolactone or eplerenone

Case 22
A 63 yo woman is referred for evaluation of hypertension. Chronic htn for years, but recently had hypertensive episode during ocular surgery, which responded poorly to medications. PMH only notable for hypertension treated with an ACE-I.

Investigations: Plasma free metanephrines were twice the normal value. A surgical intervention is planned.

In addition to aggressive IV fluid hydration, what is the best preop management?

a. Propranolol alone
b. Prazosin followed by propranolol
c. Propranolol followed by prazosin
d. Phenoxybenzamine followed by propranolol
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Pheochromocytoma

- Rare tumors
- Produce epinephrine and/or norepinephrine
- Symptoms:
  - Headaches
  - Episodic throbbing in the chest, trunk and head
  - Diaphoresis
  - Palpitations
  - Tremor, anxiety, nausea, vomiting, fatigue
  - Abdominal or chest pain
  - Weight loss
  - Cold hands and feet

Pheochromocytoma cont’d

- In ¼ of cases, hypertension is episodic
- Orthostasis usually present
- Rule of 10’s:
  - 10% normotensive
  - 10% occur in children
  - 10% are bilateral
  - 10% are malignant
  - 10% are extra-adrenal (paragangliomas)
Pheochromocytoma cont’d

- First – make BIOCHEMICAL dx:
  - 24-hr urinary metanephrine and normetanephrine or plasma free metanephrine and normetanephrine (levels usually 2-3 x normal)

- Second – if present, localize:
  - CT or MRI of the adrenal
  - If CT or MRI negative, can use $^{123}$I-MIBG to localize extra-adrenal pheo and mets

Pheochromocytoma - Tx

- Preparation for surgery:
  - Phenoxybenzamine-blocks catecholamines
  - β-blockers, only after BP is controlled, to control HR
  - Hydration

- Surgical resection by experienced surgeon – 90% cure rate

CASE 23

A 38 year old man had an abdominal CT scan for evaluation of right abdominal pain. An incidental 4 cm left adrenal mass was discovered. The patient is otherwise healthy.

What is the next step?
- a. Referral to a surgeon for laparoscopy adrenalectomy
- b. FNA of lesion to determine pathology
- c. Measurement of fractionated catecholamines and metanephrines in a 24 hr urine and a 1mg dexamethasone suppression test
- d. Repeat CT scan in 6 to 12 months to make sure that the mass has not increased in size.
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Adrenal Incidentalomas

- Prevalence:
  - ~10% of autopsies
  - 2% of pts having abdominal CT
- Prevalence increases with age

- 2 questions for evaluation:
  - Is lesion functioning or not?
  - Is lesion benign or malignant?

Incidentaloma: is it functional?

In all patients:
- Screen for pheochromocytoma:
  - 24 hr urine or plasma for fractionated metanephrines
- Screen for subclinical Cushing’s
  - 1 mg overnight dexamethasone suppression test

In patients with hypertension:
- Screen for primary aldosteronism:
  - PA/PRA ratio
**Incidentaloma: Benign or not?**

More likely to be BENIGN if:
- <4 cm
- Low density on unenhanced CT (<10 HU)
- It contains fat (suggests myelolipoma)

**Incidentaloma: Management**

CASE 24

A 62 yo man is referred because on screening laboratories, he was found to have a serum calcium of 10.8 mg/dL (8.7-10.1). He denies sx of constipation, abdominal discomfort, confusion or a history of renal stones.

What laboratory test would you order next?

a. PTHrP
b. Phosphorus, calcium and PTH
c. 25 hydroxy vitamin D
d. 1,25 di-hydroxy vitamin D
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HYPERCALCEMIA

Hypercalcemia: Clinical

- “Psychic moans, abdominal groans, stones and bones”
  - Confusion, fatigue etc
  - Constipation, abd. pain
  - Nephrolithiasis, renal insufficiency
  - Osteoporosis, osteitis fibrosa cystica (fractures, cysts, severe bone resorption)

- 85% pts asymptomatic
**Primary Hyperparathyroidism**

- ↑ PTH, ↑ Ca, ↓ Phos
- 0.4% women over 60; 2-3Xs the rate in men
- Single adenoma 80%, rest hyperplasia
- Associated with MEN1, MEN 2A, isolated familial

**Primary Hyperparathyroidism**

- **Treatment:**
  - Surgery if
    - Serum Ca >1.0 mg/dl above UNL
    - CrCl <60 ml/min
    - BMD T-score <-2.5 at any site
    - Age <50 yrs
  - If no surgery, follow with:
    - Ca and Cr yearly
    - BMD periodically
    - Calcimimetics (Cinacalcet)

**Acute Hypercalcemia Tx**

- IV Hydration with normal saline
- IV Hydration
- IV Hydration
- IV bisphosphonates if hypercalcemia of malignancy
- Calcitonin SQ can be temporizing
- Glucocorticoid if known to be 1,25 DHD mediated
CASE 25
A 56 yr old African American man presents with malaise and thirst. Examination is normal apart from some painful nodules on lower legs.

Investigations
Calcium: 11.8 (8.7-10.1), Phosphorus: 4.7 (2.4-4.6), Albumin: 4, PTH: 26 (18-73), Urine Calcium: 345 mg/24 hr (100-200 mg/d). Chest X-Ray – bilateral lymphadenopathy.

The next step is:

a. Measurement of 1,25 di-hydroxy vitamin D
b. Measurement of PTHrP
c. Treatment with a single dose of IV bisphosphonate
d. Referral to an oncologist

CASE 26
A 46 year old woman presents with chronic fatigue and cramps in her hands and feet. She has a hx of pernicious anemia and hypothyroidism due to Hashimoto’s. On examination, she has a + Chvostek’s sign. Her serum calcium is 7.9 mg/dl (8.7-10.1) and her serum phosphorus level is 4.1 (2.4-4.6) mg/dl

The most likely diagnosis is:

a. Vitamin D deficiency
b. Hypoparathyroidism
c. Renal failure
d. Hypoalbuminemia
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Hypocalcemia: Clinical
- Tetany – hallmark – tonic muscular contractions
  - Chvostek's sign
  - Trousseau's sign
- Prolonged QT interval

Hypocalcemia: Etiologies
- Hypoparathyroidism:
  - Surgical
  - Functional (low Mg)
  - Idiopathic – parathyroid Ab’s in ~ 30 %
  - Infiltrative (Wilson’s or hemochromatosis)
  - Familial (mutation in Ca sensor or PTH gene)
  TX: oral calcitriol + calcium
- Pseudohypoparathyroidism
  - Target organ unresponsiveness to PTH
  - 2 forms:
    - Isolated PTH resistance
    - Albright’s Hereditary Osteodystrophy
  TX: like hypoparathyroidism
Hypocalcemia: Etiologies cont’d

- **Vitamin D deficiency**
  TX: Vitamin D replacement

- **Abnormal calcitriol metabolism**
  - Resistance or abnormal production, e.g. hereditary rickets
  TX: oral calcitriol + calcium

- **Acute deposition or complex formation:**
  - Tumor lysis
  - Acute pancreatitis
  - Blood transfusion
  - Hungry bone syndrome

---

**CASE 27**

A 56 yr old African American man is referred because a DXA scan demonstrated T score of -2.8 at the spine. He complains of aches in his upper and lower extremities. There was no history of fractures or kidney stones. He has lactose intolerance, and is not on any medications or supplements.

**Investigations**

Calcium 9.6 (8.7-10.1), phosphorus 2.4 (2.4-4.6)

What would you do next?

- a. Give a bisphosphonate, calcium and vitamin D
- b. Check 25 OHD level
- c. Check a 1, 25 DHD level and PTH
- d. Give Raloxifene, calcium and Vitamin D
- e. Give Calcitonin, calcium and Vitamin D
Male Osteoporosis

- We currently use same definitions as for women:
  - Osteopenia: T-score < -1 and > -2.5
  - Osteoporosis: T-score ≤ -2.5
- Search for causes of secondary osteoporosis in most cases of male osteoporosis
- Tx options same as for women:
  - Bisphosphonates
  - Calcium 1500 mg/d + 800-1000 IU Vit D/day
  - Teriparatide
  - Calcitonin esp. for acute vertebral fracture pain

Secondary osteoporosis

- Definition: osteoporosis due to a treatable underlying disease.
- Evaluation for it:
  - 25 OHD level
  - Serum calcium, phosphorus, PTH
  - 24-hr urinary calcium and creatinine
  - Testosterone level
  - +/- SPEP/UPEP

CASE 28

29 yo man consults you b/c of infertility. He has a very low sperm count and would like to know why. FHx reveals infertility in cousins, uncles and aunts. Exam shows impaired sense of smell and normal external genitalia except for small testes.

Investigations
- Testosterone <200 mg/dL (250-1000 mg/dL); FSH 2 µIU/ml (N<25). CT of the head: normal

What is the most likely cause of his infertility?
- a. Panhypopituitarism
- b. Kallmann’s Syndrome
- c. Klinefelter’s Syndrome
- d. Andropause
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Male Hypogonadism DDx

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<tr>
<th>Disorder</th>
<th>Testosterone</th>
<th>LH</th>
<th>FSH</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panhypopituitarism/Kallman’s (anosmia)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Klinefelter’s: XXY</td>
<td></td>
<td></td>
<td></td>
<td>Testicular damage</td>
</tr>
<tr>
<td>Andropause</td>
<td></td>
<td></td>
<td></td>
<td>Androgen insensitivity (complete or incomplete)</td>
</tr>
</tbody>
</table>

Gynecomastia

- **Physiologic** – puberty (testicular estrogen); senescence (decreased androgen)
- **Pathologic** – Measure hCG, testosterone, LH, estradiol
  - **High estrogens** –
    - Testicular tumors (germ or Leydig cell) - ↑ hCG
    - Adrenal tumors - ↑ Estradiol
    - Image to localize (testicular U/S or CT as appropriate)
  - **High estrogen effect** –
    - Hyperthyroidism (increased SHBG) – ↑ LH, ↑ Testosterone
    - Drugs (Digoxin, estrogen)
  - **Low androgen production** –
    - Dx as per hypogonadism - ↓ Testosterone & ↓ LH
  - **Low androgen effect** – spironolactone
CASE 29
A woman has secondary amenorrhea, hirsutism and a raised serum testosterone.

Which of the following is not a likely cause
a. Late onset 21 hydroxylase deficiency
b. Cushing’s syndrome
c. Polycystic ovarian syndrome
d. Testicular feminization syndrome
e. Sertoli-Leydig cell tumor of the ovary

Hirsutism
- Hirsutism = dark hair in male pattern: face, chest, back, lower abdomen, inner thighs
- Virilization = frontal balding, voice changes, breast atrophy, clitoral enlargement, increased muscle mass
- DDx:
  - Polycystic Ovarian Syndrome
  - Idiopathic
  - adult onset congenital adrenal hyperplasia
  - adrenal & ovarian tumors
  - Cushing’s
Hirsutism cont’d

- If onset 15 - 25 yrs age & slow progression; absence of virilization → PCOS or idiopathic most likely
- Rapid progression, virilization, marked ↑ Testost. → adrenal or ovarian tumor more likely

EVALUATION:
- Testosterone, androstenedione, DHEA-S
- 17-hydroxy progesterone
  - <3 ng/ml (200 ng/dL) – normal
  - If abnormal, measure post ACTH stimulation
- 1mg overnight dexamethasone suppression test
  - If concerned about Cushing’s

Hirsutism - Treatment

- OCP’s –
  - Estrogen
    - ↓ LH & FSH secretion
    - ↓ ovarian androgen production.
    - Combination with an anti androgen progestogen (e.g. Yasmin) ideal
- Anti-androgens – spironolactone
- 5 alpha reductase inhibitor – finasteride
- “Mechanical Removal” - depilation, wax, electrolysis, laser etc.

CASE 30

A 44 year old woman presents with amenorrhea and galactorrhea.
PMH: kidney stones
Labs: PRL 270 ng/ml (<20)
MRI: 1.2 cm sellar mass
FH: peptic ulcer disease; nephrolithiasis

What other sites should be considered for possible neoplasia in this patient?

a. Thyroid and pancreas
b. Parathyroid and pancreas
c. Thyroid and colon
d. Thyroid and parathyroid
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---

**MEN 1 (Wermer's)**

- HyperParathyroidism – hyperplasia of parathyroids
- Enteropancreatic tumors – gastrinomas, insulinomas
- Pituitary tumors – prolactinoma, GH, nonfunctional, ACTH
- Others – carcinoid, adrenal adenomas, subcutaneous lipomas, facial angiofibromas
- Autosomal dominant, MENIN gene mutation

---

**MEN 2A (Sipple’s syndrome)**

- Medullary carcinoma of the thyroid
- Pheochromocytoma
- Hyperparathyroidism
- Mutations in RET proto-oncogene
- Autosomal dominant
MEN 2B

- Medullary carcinoma of the thyroid
- Pheochromocytoma
- Marfanoid habitus
- Mucosal neuromas
- Ganglioneuromatosis of the bowel
- Mutations in RET protooncogene
- Autosomal dominant

Best of luck!!!

Additional Material

- In this section are slides covering material that might be of help when studying, but that is more detailed than we can cover in the talk.
- Also included are a couple of extra questions
### Pituitary Hormones and Their Function

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Increased by</th>
<th>Decreased by</th>
<th>Excess</th>
<th>Deficiency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>Thirst, high serum osmolality</td>
<td>Low serum osmolality, low serum K⁺</td>
<td>SIADH</td>
<td>None</td>
<td>X</td>
</tr>
<tr>
<td>ACTH</td>
<td>CRH, Stress</td>
<td>High cortisol</td>
<td>Cushings syndrome</td>
<td>Adrenal insufficiency</td>
<td>X</td>
</tr>
<tr>
<td>TSH</td>
<td>T₄, T₃</td>
<td>High T₄, low T₃</td>
<td>Hypothyroidism</td>
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<td>X</td>
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<td>LH/FSH</td>
<td>Gonadal sex steroids</td>
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<td>Hypogonadism</td>
<td>Hypogonadism</td>
<td>X</td>
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<td>GH</td>
<td>GHRH, hypogonadism, dopamine</td>
<td>Somatostatin</td>
<td>Childhood gigantism</td>
<td>Adult: short stature, adult: poor sense of well-being</td>
<td>X</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Pregnancy, nursing, TRH, stress</td>
<td>Dopamine</td>
<td>Galactorrhea, hypogonadism</td>
<td>Inability to lactate</td>
<td>X</td>
</tr>
</tbody>
</table>

### Hypopit. Etiologies – 9 I’s
- Invasive – tumors, metastasis
- Infarction – Sheehan’s, apoplexy
- Iatrogenic – radiation, surgery
- Infiltrative – sarcoid, hemochromatosis, histiocytosis X
- Injury – head trauma (also can see DI)
- Immunologic – lymphocytic hypophysitis
- Infections – TB, syphilis or fungi
- Idiopathic
- Isolated –
  - Kallman’s – GnRH deficiency with anosmia – X-linked dominant – decreased expression of KAL 1

### Pituitary Tumors – Ddx
- Not all lesions in the sella are pituitary adenomas.
- Other possibilities include:
  - Craniopharyngioma
  - Meningioma
  - Primary malignancy (germ cell tumors, sarcomas, chordomas, lymphomas)
  - Metastases (breast and lung cancer)
  - Cysts
  - Infections
  - Lymphocytic Hypophysitis
Diagnosis of Acromegaly

- Oral glucose tolerance test
  - 100 g glucose given
  - 60 minutes GH<1 ng/ml rules out acromegaly
- Random GH level not helpful!

Diabetes Insipidus Ddx

- **Central DI** – deficient secretion of ADH by pituitary due to surgery, trauma, tumors, cysts, histiocytosis X, granulomas, infections, autoimmune, familial, DIDMOAD (DI, DM, Optic Atrophy, Deafness), pregnancy (↑ plasma vasopressinase)
- **Nephrogenic DI** – resistance to ADH actions, seen in CRF, hypokalemia, hypercalcemia, sickle cell, Sjogren’s, lithium, foscarnet, cidofovir and other drugs (demeclocycline, colchicine, methoxyflurane), familial (V2 receptor gene defect, aquaporin-2 gene defect)
- **Primary polydipsia** (Psychogenic polydipsia)

Thyroid Antibody Details

- TPO Ab’s: in 50-80% Graves’ pts & >90% pts with Hashimoto’s
- Tg Ab’s: 50-60% Graves’ pts & 90% pts with Hashimoto’s
- TSH rcptr stimulating immunoglobulins (TSI): 80-95% Graves’ pts.
  - Also positive in euthyroid Graves’ ophthalmopathy
<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
<th>Clinical Findings</th>
<th>Tests</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute Thyroiditis</td>
<td>Viral</td>
<td>Hyperthy then hypothy. Tender, large thyroid, fever</td>
<td>High ESR; no thy Ab's; low RAI uptake</td>
<td>NSAIDs, tylenol +/- steroids.</td>
</tr>
<tr>
<td>Hashimoto's Thyroiditis</td>
<td>Autoimmune</td>
<td>Hypothyroid Painless +/- goiter</td>
<td>95% + TPO</td>
<td>L-T4</td>
</tr>
<tr>
<td>Suppurative Thyroiditis</td>
<td>Bacteria&gt; other infcs</td>
<td>Fever, neck pain, tender</td>
<td>Normal TFTs; No uptake on RAIU; + cux</td>
<td>Antibiotics and drainage</td>
</tr>
<tr>
<td>Riedel's Thyroiditis</td>
<td>Fibrosis; rare</td>
<td>Compressive sx: stridor, SVC syndrx</td>
<td>67% + Ab's</td>
<td>Surgery</td>
</tr>
<tr>
<td>Postpartum Thyroiditis</td>
<td>Lymphocytic infiltration. Up to 10% pregnancies</td>
<td>Small, nontender thyroid</td>
<td>Hyper or hypo. Ab's often +, low RAIU</td>
<td>No tx</td>
</tr>
</tbody>
</table>

**Thyroid Nodule Evaluation & Treatment**

- **Thyroid Nodule**
  - Hypothyroid or euthyroid
  - Hyperthyroid

- **FNA**
  - Malignant
  - Follicular or inconclusive
  - Benign

- **RAIU/scan**
  - Surgery +/- RAI
  - Observe
  - Cold Nodule
  - Hot Nodule

**Cushing's Diagnosis**

**Step 1:** confirm excess cortisol secretion

- **Overnight Dexamethasone Suppression Test:**
  - 1-mg dexa (po) at 11pm; check serum cortisol at 8am
  - Cortisol <1.8 mcg/dL rules out Cushing’s syndrome

- **24-hr Urine Free Cortisol**
  - >100 mcg in 24-hr suggests cortisol excess
  - If clinical suspicion is high, but test is normal, repeat
Cushing's Diagnosis cont'd

Step 2: determine if ACTH dep. or indep.
- Check ACTH level
  - If low (<5 pg/mL) → excess cortisol coming from ADRENALS
  - If high (>10 pg/mL) → must locate source

Step 3: localize tumor with imaging
- If adrenal source suspected: CT Adrenals
- If central source suspected: MRI pituitary

Cushing's Diagnosis cont'd

Step 4: ancillary testing, if no source localized:
- Inferior petrosal sinus sampling (IPSS)
  - If central gradient: pituitary source → pituitary surgery
  - If peripheral gradient: ectopic source → further diagnostic evaluation required

Cushing's Diagnosis con't

ACTH

Low (<5) Adrenal

High (>10 pg/mL) Pituitary or Ectopic

CT Adrenals

MRI pituitary

Petrosal Sinus ACTH

Peripheral

Central

Ectopic ACTH-producing tumor Pituitary source
Pseudo-aldosteronism

- HTN & ↓K⁺, but with low PRA & aldosterone
  - Liddle’s syndrome – rx with amiloride
    - Constitutive activation of Na channels on distal renal tubules
  - Enzyme defects – rx with spironolactone:
    - 11β-hydroxysteroid dehydrogenase defect so cortisol is not being inactivated into cortisone
  - Black licorice

Secondary Osteoporosis Ddx

<table>
<thead>
<tr>
<th>Endocrine Causes:</th>
<th>Marrow/hematologic disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cushing’s syndrome</td>
<td>- Multiple myeloma</td>
</tr>
<tr>
<td>- Eating disorders</td>
<td>- Leukemia/lymphomas</td>
</tr>
<tr>
<td>- Hypogonadism (male or female)</td>
<td>- Systemic mastocytosis</td>
</tr>
<tr>
<td>- Hyperprolactinemia (by inducing hypogonadism)</td>
<td>- Hemophilia</td>
</tr>
<tr>
<td>- Hyperthyroidism</td>
<td>- Thalassemia</td>
</tr>
<tr>
<td>- Hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>- Vitamin D deficiency</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI Disorders:</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Liver disease</td>
<td>- Immobilization</td>
</tr>
<tr>
<td>- Malabsorptive conditions (mediated primarily via vitamin D deficiency):</td>
<td>- Alcohol abuse</td>
</tr>
<tr>
<td>- Gastrectomy</td>
<td>- Tobacco use</td>
</tr>
<tr>
<td>- Inflammatory bowel disorders</td>
<td>- Osteogenesis imperfecta</td>
</tr>
<tr>
<td>- Gastric bypass</td>
<td>- Rheumatoid arthritis</td>
</tr>
<tr>
<td>- Pancreatic insufficiency</td>
<td>- Ankylosing spondylitis</td>
</tr>
</tbody>
</table>

CASE 31
A 59 yo woman has the following results on routine testing:
Na: 136, K: 4.3, Calcium 10.8 (8.1-10.5), Albumin 4.0, Phosphorus 2.4 (2.4-4.6), PTH 68 ng/L (18-73), 24 hr urinary calcium 35 mg/d (100-200).

The next step is to:
a. Perform parathyroid adenoma localization studies, such as 99m Tc-sestamibi scanning, u/s, MRI or CT scan
b. Refer to surgeon
c. Get a family history and if necessary check calcium in family members
d. Treat with a bisphosphonate or SERM
CASE 31
A 59 yo asymptomatic woman has the following results on routine testing:
Normal Na and K, Calcium 10.8 (8.1-10.5), Albumin 4.0, Phosphorus 2.4 (2.4-4.6), PTH 68 ng/L (18-73), 24 hr urinary calcium 35 mg/d (100-200).

The next step is to:
- a. Perform parathyroid adenoma localization studies (99m Tc-sestamibi scanning, u/s, MRI or CT scan)
- b. Refer to surgeon
- c. Get a family history and if necessary check calcium in family members
- d. Treat with a bisphosphonate or SERM

Answer: C

Familial Benign Hypocalciuric Hypercalcemia (FBHH)
- Mutation in calcium sensor
- Autosomal dominant inheritance
- Lifelong asymptomatic hypercalcemia
- Urine Ca < 50 mg/24 hr
- Calcium creatinine clearance ratio < 0.01
  \[
  \text{urine Ca} \times \text{Serum Creat} \\
  \text{serum Ca} \times \text{Urine Creat}
  \]
- \( \rightarrow \text{No need for treatment!} \)

QUESTION 32
Match the etiology of hypercalcemia on the right with the appropriate answer on the left (each letter answer may be used once, more than once, or not at all):

| A) ↓PTH, ↓n1Ca++ | 1. Exogenous Vit D excess |
| B) ↓PTH, ↑Ca++, ↓PTHrP | 2. Primary Hyperparathyroidism |
| C) ↑PTH, ↑Ca++, ↓Phos | 3. Secondary Hyperparathyroidism |
| D) ↓25-Vitamin D | 4. Sarcoidosis |
| E) ↑1,25-Vitamin D | 5. Squamous Cell Lung Cancer |
**QUESTION 32**

Match the etiology of hypercalcemia on the right with the appropriate answer on the left (each letter answer may be used once, more than once, or not at all):

A) ↑PTH, ↓n-1 Ca**
B) ↓PTH, ↑Ca**, ↑PTHrP
C) 1PTH, 1Ca**, ↓Phos
D) 125-Vitamin D
E) 11.25-Vitamin D

Answers: 1D; 2C; 3A; 4E; 5B

<table>
<thead>
<tr>
<th>Class</th>
<th>Names</th>
<th>Dosing</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride, glipizide, glyburide, etc.</td>
<td>QD or BID</td>
<td>Hypoglycemia</td>
<td>Different medications have varying degrees of renal or liver metabolism.</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>BID or TID</td>
<td>GI (nausea, diarrhea, ↓ appetite), rare hypoglycemia</td>
<td>Helps weight loss. Lactic acidosis risk increased if GFR &lt; 1.5, CHF, severe respiratory disease, liver disease or if age &gt; 80 yrs.</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide, nateglinide</td>
<td>Pre-meal (TID)</td>
<td>Hypoglycemia</td>
<td>Short action for postprandial hyperglycemia.</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone, pioglitazone</td>
<td>QD</td>
<td>Fluid retention and edema, rare hypoglycemia</td>
<td>V. rare liver dz - check LFTs at start and during rx. Do not use in CHF.</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Miglitol, acarbose</td>
<td>TID</td>
<td>Gas, bloating, diarrhea</td>
<td>Start low and gradually increase the dose. Should not be used in people with GI problems.</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Exenatide</td>
<td>SQ BID</td>
<td>GI: N/V, diarrhea</td>
<td>Promotes wt loss; only w/ sulfonylureas or metfor.</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>QD</td>
<td>URI, naso-pharyngitis, H/A</td>
<td>Weight-neutral; prevent breakdown of incretins</td>
</tr>
</tbody>
</table>

**CASE 33**

A 30 year old woman with type 1 diabetes presents with fatigue. She has a history of recurrent diarrhea and hypothyroidism due to Hashimoto’s.

On examination: she is pale and has no hyperpigmentation; the thyroid gland feels normal.

Labs: TSH: 0.9 (0.5-4.7); HbA1c: 7.2 %; Hemoglobin: 10, MCV: 75 (83-95)

Which of the following is the most appropriate next step in her evaluation?

a. Plasma ACTH
b. Iron/TIBC/Ferritin
c. Iron/TIBC/Ferritin and antibodies to tissue transglutaminase
d. Cosyntropin stimulation test
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c. Iron/TIBC/Ferritin and antibodies to tissue transglutaminase
d. Cosyntropin stimulation test

Answer: C

---

APS I

<table>
<thead>
<tr>
<th>Alternative Name</th>
<th>APS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>APCED (Autoimmune Polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome)</td>
<td>Schmidt's Syndrome</td>
</tr>
</tbody>
</table>

| Genetics | | | |
|----------|----------|----------|
| AR       | Mutations in AIRE (autoimmune regulator gene) | Linked to HLA-DR3 or HLA-DR4 |
|          | Female-to-male ratio = 3:1 | |

| Endocrine manifestations | | | |
|--------------------------|----------|----------|
| Hypoparathyroidism        | – 90%    | Hypoadrenalism | – 70% |
| Hypoadrenalism            | – 60%    | Hypogonadism   | – 45% |
| Hypothyroidism            | – 12%    | Hypothyroidism | – 50% |

| Non-endocrine manifestations | | | |
|-----------------------------|----------|----------|
| Mucocutaneous candidiasis  | – 75%    | Pernicious Anemia | – 15% |
| Malabsorption               | – 25%    | Vitiligo       | – 4%  |
| Alopecia                    | – 20%    | Celiac disease | – 3%  |
| Pernicious Anemia           | – 15%    | Autoimmune hepatitis | – 10% |
| Autoimmune hepatitis        | – 10%    | | |
| Venous thrombosis           | – 15%    | | |
| | | | |

---

CASE 34
Which of the following is not a feature of hyperosmolar diabetic coma?

a. Venous thrombosis
b. Coma occurs when calculated serum osmolality exceeds 340
c. Ketosis
d. Rhabdomyolysis
e. Focal neurological signs

---

58
CASE 34
Which of the following is not a feature of hyperosmolar diabetic coma?

a. Venous thrombosis
b. Coma occurs when calculated serum osmolality exceeds 340
c. Ketosis
d. Rhabdomyolysis
e. Focal neurological signs

Answer: C

Hyperthyroidism: Graves’
Eye Changes of Graves’ pre and post treatment for hyperthyroidism

Hyperpigmentation characteristic of primary adrenal insufficiency
PCOS

- Polycystic Ovarian SYNDROME dx:
  - Oligo or amenorrhea - anovulation
  - Clinical or biochemical hyperandrogenism
    - Mildly increased Testosterone, DHEAS
  - Exclusion of other causes of ↑androgen
  - Also associated with:
    - Hirsutism
    - Infertility
    - Insulin resistance
    - Obesity
    - ↑ risk of DM2

Hyperthyroidism: Graves’

- Pretibial Myxedema: peau d’orange appearance
- Pathognomonic of Graves’ Disease

Hyperthyroidism: Graves’

- Onycholysis
**123I Scan in Thyroiditis**

**Thyroid Ultrasound**

- Uses:
  - To confirm thyroid nodule
  - To measure size and determine characteristics of nodule
  - To follow thyroid cancer patients for local recurrence
- Not routinely done in the evaluation of hyper or hypothyroidism

**QUESTION 35**

With respect to Graves' disease which of the following is **false**:

a. Exophthalmos can occur in the absence of hyperthyroidism
b. Men are affected more often than women
d. Asian males can present with a sudden attack of flaccid paralysis
e. $I^{131}$ therapy can exacerbate the eye disease
QUESTION 35
With respect to Graves’ disease which of the following is false:

a. Exophthalmos can occur in the absence of hyperthyroidism
b. Men are affected more often than women
d. Asian males can present with a sudden attack of flaccid paralysis
d. $^{131}$I therapy can exacerbate the eye disease

Answer: B

Hyperprolactinemia Cont’d

Pharmacologic:

- Estrogen
- Dopamine antagonists (phenothiazines, haloperidol, risperidone, metoclopramide, methylthopropion, opioids, amoxapine)
- Monoamine oxidase inhibitors
- Cimetidine and Ranitidine
- SSRI’s
- TCA’s
- Verapamil
- Liquorice

Hyperprolactinemia: Treatment

- Medical – 1st line in most cases
  - Dopamine agonists: bromocriptine or cabergoline
    - SE: nausea, fatigue, nasal stuffiness and postural hypotension
  - Restores fertility and gonadal function in most patients
  - Leads to tumor shrinkage
Hyperprolactinemia: Treatment

- **Surgical:**
  - For patients intolerant or resistant to medications
  - If need urgent decompression of the sella turcica for visual field defects unresponsive to trial of dopamine agonists

---

CASE 36

Which one of the following laboratory findings is true in a patient with Cushing’s syndrome.

- a. ACTH would be high if an adrenal adenoma is the cause
- b. The am cortisol would be very low (<1.8ug/dl) following a 1 mg dexamethasone suppression test
- c. The diurnal rhythm of cortisol secretion is lost
- d. Hyperkalemia and metabolic alkalosis may be noted

**Answer:** C
CASE 37

32 yo man presents with enlargement and tenderness of breasts for 6 mo. He has been on a β-blocker for htn for 3 yrs. On exam, BP 128/82, bilateral breast enlargement but no other abnormalities.

Laboratory data:
Testosterone: 600 ng/dL (185-800); Estradiol 88 pg/mL (10-50); LH 2.6 IU/mL (2-12); FSH: 1.7 IU/mL (1-8);
hCG: 3500 IU/L (<2)

What is the most appropriate next diagnostic test in this patient:

a. Breast ultrasound
b. MRI of the pituitary gland
c. Ultrasonography of the testes
d. Peripheral blood karyotype
e. Prolactin measurement

Answer: C

Answers

1D; 2D; 3C; 4D; 5A; 6D; 7D; 8C; 9B; 10D; 11A; 12C; 13D; 14D; 15D; 16D; 17C; 18C; 19D; 20C; 21A; 22D; 23C; 24B; 25A; 26B; 27B; 28B; 29D; 30B; 31C; 32: 1D, 2C, 3A, 4E, 5B, 33C, 34C; 35B; 36C, 37C.