The Endocrine System

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PANCE/PANRE Review Course

The Endocrine System

• Disease of the Pituitary Gland
• Diseases of the Thyroid
• Disease of the Adrenal Glands
• Diabetes Mellitus
• Lipid Disorders

Pituitary Gland

• Functional Anatomy
  – Anterior lobe secretes trophic hormones
  – Posterior lobe secretes vasopressin and oxytocin
• Hypothalamic Pituitary Axis
  – Negative feedback control at pit. and hypothalamus
• Pathology
  – Pituitary adenoma
  – Sellar mass
  – Hypopituitarism
PITUITARY ANATOMY

- Small pea-sized gland at the base of brain
- Located in the Sella Turcica, surrounded by bone
- Functions as "The Master Gland"
- Attached below hypothalamus by stalk
- Large anterior lobe (adenohypophysis)
- Smaller posterior lobe (neurohypophysis)
- The optic chiasm lies directly above
- Supplied by internal carotid artery

Hypothalamic Pituitary Axis

- Hypothalamus sends releasing hormones (RH) to the median eminence
- Hypophyseal portal system takes RH directly to anterior pituitary
- Anterior Pituitary gland secretes trophic hormones to the thyroid gland, adrenal glands, and gonads
- The glands respond by releasing the active hormones
- Negative feedback mechanism finishes the loop

Anterior Pituitary Trophic Hormones

"Turn-on" other endocrine glands
1. TSH -> Thyroid
2. ACTH -> Adrenal Cortex
3. FSH -> Follicles in gonads
4. LH -> as above with some exceptions

NON-Trophic Anterior Pituitary hormones:
- Growth Hormone
- Prolactin
Growth Hormone

- Release from Ant. Pit. promoted by GHRH, suppressed by somatostatin
- Converted in liver to insulin-like growth factor (IGFI) which promotes growth
- Metabolic effect is “anti-insulin”
  - Stimulates hepatic gluconeogenesis
  - Promotes muscle growth, increases lipolysis
  - GH excess can lead to type 2 DM (high risk with GH “supplementation” to prevent aging)

Growth Hormone and Aging

- With normal aging GH levels decline
- GH supplementation shown to:
  - Increase protein deposition in the body, especially in the muscles
  - Decrease fat deposits
  - Bring out a feeling of increased energy
- Increase risk of insulin resistance, arthralgias, gynecomastia
Prolactin

- Synthesized by lactotrophs in Ant. Pituitary
- Unique control mechanism—> **Dopamine inhibits** prolactin secretion from Ant. Pit.
- Estrogen, TRH, and GHRH positively effect prolactin secretion
- Excess can be caused by lactation, tumors, drugs, hypothyroidism, hypothalamic dysfunction

Types of Pituitary Adenomas and their clinical consequence

<table>
<thead>
<tr>
<th>Cell type of adenoma</th>
<th>Clinical condition</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinoma</td>
<td>Hypogonadism, galactorrhea</td>
<td>25-40</td>
</tr>
<tr>
<td></td>
<td>Headache, bitemporal hemianopsia</td>
<td></td>
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<tr>
<td>Somatotrophs (Growth Hormone)</td>
<td>Gigantism before puberty, acromegaly after</td>
<td>10-15</td>
</tr>
<tr>
<td>Corticotroph (ACTH)</td>
<td>Cushing’s disease with elevated ACTH (hyperpigmentation)</td>
<td>10-15</td>
</tr>
<tr>
<td>Gonadotroph (FSH/LH)</td>
<td>90% of “silent” adenomas/can lead to hypopituitarism from mass effect</td>
<td>10-15</td>
</tr>
<tr>
<td>Thyrotroph (TSH)</td>
<td>Hyperthyroidism</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Work-up of Pituitary Adenoma

- Somatotrophic (Growth Hormone) adenoma
  - serum IG-F elevated, no suppression with glucose tolerance test
- Corticotrophic (ACTH) adenoma
  - Cushing’s disease—> elevated 24 hr urinary cortisol, suppression seen on **high dose** dexamethasone suppression test only
- Lactotrophic (Prolactin) adenoma
  - High prolactin level
Treatment of pituitary adenomas

- Prolactinomas
  - Dopamine agonists (bromocriptine)
- Somatotropinomas
  - Octreotide is a somatostatin analog
- Corticotropinomas
  - Metyrapone is a peripheral inhibitor
- Surgical removal of the adenoma
  - Endoscopic with transphenoidal approach
  - Stereotactic radiotherapy

GH Abnormalities

- GH excess
  - Elevated IGF-1 levels
  - Somatotroph adenoma of Ant. Pit. -> overproduction of GH
    - Before puberty -> Gigantism
    - After puberty -> Acromegaly
      - Bones thicken and soft tissues enlarge
- GH deficiency
  - Dwarfism -> deficiency during childhood
  - Treat with synthetic growth hormone injections

Prominent Jaw/Brow
Acromegaly: Excess GH after puberty

- Enlargement of extremities
  - Hands doughy / large hands
- Coarse facial features
  - Prominent mandible, brow, nose, lips, tongue
- Coarse, oily, thick skin
- Organomegaly

Growth Hormone Deficiency (GHD)
Dwarfism in children

- Defined as height 2.25 standard deviations below the mean (1st percentile)
- Genetic (Familial) short stature
- Constitutional short stature
- Idiopathic Short Stature (ISS)

GROWTH HORMONE REPLACEMENT

- Somatotropin given as daily SQ injection until bone fusion (Bone Age)
- May not need further treatment as adults, consider repeating stimulation test
- Side effects include headaches, carpal tunnel, arthralgias, and edema
- Monitor for scoliosis
Etiology of Hypopituitarism

- Pituitary diseases
  - Mass lesions - pituitary adenomas, other benign tumors, cysts
  - Pituitary surgery or radiation
  - Infiltrative lesions - lymphocytic hypophysitis, hemochromatosis
  - Infarction - Sheehan syndrome (post partum)
  - Apoplexy
  - Genetic diseases - pit-1 mutation

Etiology of Hypopituitarism (cont.)

- Hypothalamic diseases
  - Mass lesions - benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc.)
  - Radiation - for CNS and nasopharyngeal malignancies
  - Infiltrative lesions - sarcoidosis, Langerhans cell histiocytosis
  - Trauma - fracture of skull base

Anterior Hypopituitarism

- Adrenocorticotropic hormone deficiency: reduced adrenal secretion of cortisol, testosterone, and epinephrine; aldosterone secretion remains intact.
- Growth hormone (GH) deficiency: short stature in children; asthenia, obesity, and increased cardiac mortality in adults.
- Prolactin deficiency: inhibition of postpartum lactation.
- Thyroid-stimulating hormone (TSH) deficiency: secondary hypothyroidism.
- Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency: hypogonadism and infertility in men and women.
Diabetes Insipidus

- A condition of intense thirst (polydipsia) and excessive urination (polyuria) owing to the kidneys’ inability to conserve water as they filter blood due to vasopressin (ADH) defect
- Most commonly, this results from decreased pituitary secretion of vasopressin (central diabetes insipidus [DI]) or failure of response to vasopressin (nephrogenic DI).
- Central DI Etiology: Head trauma, intracranial neoplasm, infection, following neurosurgery
- Nephrogenic DI Etiology: Drug induced (amphotericin B, colchicine, demeclocycline, foscamet, gentamicin, lithium, loop diuretics), hypercalcemia

Diabetes Insipidus Testing

<table>
<thead>
<tr>
<th></th>
<th>Central DI</th>
<th>Nephrogenic Diabetes Insipidus</th>
<th>Psychogenic Polydipsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma osmolality</td>
<td>low</td>
<td>High if thirst impaired</td>
<td>normal</td>
</tr>
<tr>
<td>Plasma Sodium</td>
<td>High normal</td>
<td>High if thirst impaired</td>
<td>low</td>
</tr>
<tr>
<td>Plasma vasopressin</td>
<td>low</td>
<td>Normal/high</td>
<td>low</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>Less than plasma osmolality</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

Treatment of Diabetes Insipidus

- Central DI: Desmopressin (DDAVP), Carbamazipine
- Nephrogenic: Thiazide diuretics, indomethacin, amiloride (combo)
Thyroid Gland

- Controls metabolism
- Mainly secretes thyroxine (T4)
- Responds to Thyroid Stimulating Hormone (TSH)
- Synthesized from tyrosine in a complicated process requiring uptake, oxidation, and organification of iodine

Thyroid Gland Hormones

- Thyroxine (T4) - 91%
  - Solely produced in thyroid gland
- Triiodothyronine (T3) - 7%
  - Four times as potent as T4
  - Much shorter half-life
  - 80% formed by T4 deiodination in most tissues
  - Two types of deiodinase enzymes in the periphery convert T4 to T3
- Reverse T3 - 2%
  - Not active in humans

Hypothalamic-Pituitary control

- TRH is secreted by the hypothalamus and stimulates the secretion of TSH by the anterior pituitary.
- TSH increases both the synthesis and the secretion of thyroid hormones
- Chronic elevation of TSH causes hypertrophy of the thyroid gland.

Hypothalamic-Pituitary-Thyroid Axis
**Thyroid Function Tests**

<table>
<thead>
<tr>
<th>Serum TSH</th>
<th>Serum Free T4</th>
<th>Serum T3</th>
<th>Assessment</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Normal</td>
<td>Low</td>
<td>Normal or high</td>
<td>Euthyroid: triiodothyronine therapy</td>
</tr>
<tr>
<td>Normal</td>
<td>Low normal or low</td>
<td>Normal or high</td>
<td>Euthyroid: thyroid extract therapy</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Normal or low</td>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td>Subclinical hypothyroidism</td>
</tr>
<tr>
<td>Low</td>
<td>High or normal</td>
<td>High</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Subclinical hyperthyroidism</td>
</tr>
</tbody>
</table>

**Screening for Thyroid Disease**

- Serum TSH normal -> no further testing performed
- Serum TSH high -> degree of TSH elevation correlates with the degree of hypothyroidism
- Serum TSH low -> free T4 and T3 added to determine the degree of hyperthyroidism
- United States Preventive Services Task Force **does not** recommend routine screening for thyroid disease in children or adults

**Subclinical Hypothyroidism**

(elevated TSH with normal free T4)

- Prevalence ranges from 4 to 15 percent
- Rises with age, is higher in females than males, and is lower in blacks than in whites
- Prevalence is determined by the upper limit of normal for serum TSH (<10)
  - If the upper limit of normal rises with age, as appears to be the case, then the prevalence may not be as high as has been previously thought
- Cumulative incidence of overt hypothyroidism ranges from 33 to 55 percent
Management of subclinical hypothyroidism

- virtually all experts recommend treatment of patients with serum TSH concentrations >10
- the routine treatment of asymptomatic patients with TSH values between 4.5 and 10 remains controversial
- Goal of treatment 0.5 to 2.5 in young, 3 to 5 in elderly
  - Lower values increase risk of osteoporosis, angina
- Initiate with low dose (25 to 50 mcg daily) and monitor TSH

Thyroid Hormone Actions: Growth

- Attainment of adult stature requires thyroid hormone.
- Thyroid hormones act synergistically with growth hormone and somatomedins to promote bone formation.
- Thyroid hormones stimulate bone maturation as a result of ossification and fusion of the growth plates.
  - In thyroid hormone deficiency, bone age is less than chronologic age.

Central nervous system (CNS)

- Maturation of the CNS requires thyroid hormone in the perinatal period, thyroid hormone deficiency causes irreversible mental retardation.
- Hyperthyroidism causes hyperexcitability and irritability.
- Hypothyroidism causes listlessness, slowed speech, somnolence, impaired memory, and decreased mental capacity.
Congenital hypothyroidism
- 1:3000 newborns (85% sporadic/15% hereditary)
- Screen newborn with T4, TSH follow-up
- Infants usually appear normal at birth
  - T4 crosses placenta
- Cretinism is mental retardation, poor growth
  - results from congenital lack of a thyroid gland
  - failure of the thyroid gland to produce thyroid hormone
    - because of a genetic defect of the gland (congenital cretinism)
    - from iodine lack in the diet (endemic cretinism).

Functions of thyroid hormones
- Autonomic nervous system
  - up-regulates β1-adrenergic receptors in the heart
  - useful adjunct therapy for hyperthyroidism is treatment with a β-adrenergic blocking agent
- Basal metabolic rate (BMR)
  - O2 consumption and BMR are increased
  - The overall effect of thyroid hormone is catabolic
- Cardiovascular and respiratory systems
  - Resp. rate, Heart rate and stroke volume are increased
  - Can lead to angina, atrial fibrillation and heart failure

Thyroid pathology
- Hyperthyroidism
  - With a normal or high radiiodine uptake (Graves)
  - With a near absent radiiodine uptake (exogenous source)
  - Hyperthyroidism during pregnancy
- Hypothyroidism
  - Chronic autoimmune thyroiditis
  - Iatrogenic
  - Thyroidectomy
  - Radiiodine therapy or external irradiation
  - Iodine deficiency or excess
  - Subclinical hypothyroidism
- Thyroid Cancer
Hyperthyroidism with a normal or high radioiodine uptake

- Autoimmune thyroid disease
  - Graves' disease
- Autonomous thyroid tissue
  - Toxic adenoma in anterior pituitary -> TSH excess
  - Toxic multinodular goiter
- TSH-mediated hyperthyroidism
  - TSH-producing pituitary adenoma
  - Non-neoplastic TSH-mediated hyperthyroidism

Graves Disease

- Affects approximately 0.5% of the population
- Cause of 50 to 80% of cases of hyperthyroidism
- Thyroid-stimulating immunoglobulins
  - circulating IgG antibodies that bind to and activate the TSH receptor
  - mimics the effects of TSH
- Excess production of T4 not turned off despite very low TSH levels

EXOPHTHALMOS

- 20-25% of hyperthyroid patients develop bulging eyes
  - Most, but not all, are related to Grave's Disease
  - 20% start before, 40% concurrent, and 20% after treatment
- Upper lid lag on downward gaze
- Each eye can be affected differently
- May see weak upward gaze, diplopia
- Excess tearing, photophobia, gritty feel
- Treatment with a glucocorticoid, and/or orbital irradiation, and/or orbital decompression surgery to reduce inflammation in the periorbital tissue
Grave’s Clinical Features

• Nervousness, insomnia, irritability
• Hand tremor, hyperactivity, tremulousness
• Excessive sweating, heat intolerance
• Weight Loss (despite appetite)
• Diarrhea, frequent defecation
• Palpitations (tachyarrhythmias)
• Muscle weakness
• Menstrual irregularities

Graves Treatment Options

• Antithyroid drugs that block thyroid peroxidase
  – Propylthiouracil (PTU)
    • used in severe cases, pregnancy and breast feeding
  – Methimazole (Tapazole) preferred
    • works quicker, once daily dose, less hepatotoxicity
• Radioiodine is administered as sodium 131-I
  – Rapidly incorporated into the thyroid and its beta-emissions result in extensive local tissue damage.
  – The net effect is ablation of thyroid function over a period of 6 to 18 weeks.
    • Need to follow closely for development of hypothyroidism

Surgical- Thyroidectomy

• Indicated for large obstructing glands, malignant nodules, or pregnancy
• Must be euthyroid before surgery
  • Potassium iodide is given pre-op to reduce vascularity
  • Thionamides alone are sufficient to achieve euthyroidism in approximately three to eight weeks
• Complications:
  – Recurrent laryngeal nerve damage-> hoarseness
  – Bleeding
  – Hypoparathyroidism in up to 20%
    – hypocalcemia-> Chvostek's and Trousseau's signs
Thyroid Storm

- Rare complication of thyrotoxicosis
- Precipitating factors:
  - Stressful illness - thyroid surgery
  - DKA - infection
  - Severe trauma - childbirth
- High mortality rate: 20% pts. (coma or die)
- Treat with beta blockers, PTU, iodine, glucocorticoids

Hypothyroid Symptoms & Signs

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowing of metabolic</td>
<td>Fatigue and weakness</td>
<td>Slow movement and</td>
</tr>
<tr>
<td>processes</td>
<td>Cold intolerance</td>
<td>slow speech</td>
</tr>
<tr>
<td></td>
<td>Dyspnea on exertion</td>
<td>Delayed relaxation of tendon</td>
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<tr>
<td></td>
<td>Weight gain</td>
<td>reflexes</td>
</tr>
<tr>
<td></td>
<td>Cognitive dysfunction</td>
<td>Bradycardia</td>
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<tr>
<td></td>
<td>Mental retardation</td>
<td></td>
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<tr>
<td></td>
<td>(infantile onset)</td>
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<tr>
<td></td>
<td>Constipation</td>
<td></td>
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<tr>
<td></td>
<td>Growth failure</td>
<td></td>
</tr>
<tr>
<td>Accumulation of matrix</td>
<td>Dry skin</td>
<td>Coarse skin</td>
</tr>
<tr>
<td>substances</td>
<td></td>
<td>Puffy facies and loss of</td>
</tr>
<tr>
<td></td>
<td>Hoarseness</td>
<td>eyebrows</td>
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<tr>
<td></td>
<td>Edema</td>
<td>Periorbital edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enlargement of the tongue</td>
</tr>
</tbody>
</table>

Etiology of Hypothyroidism

- **Primary hypothyroidism** (thyroid gland dysfunction): >90% of the cases of hypothyroidism
- **Hashimoto’s thyroiditis** is the most common cause of hypothyroidism after age 8
- Previous treatment of hyperthyroidism (radioiodine therapy, subtotal thyroidectomy)
- Subacute thyroiditis often causes transient hypothyroidism
- Radiation therapy to the neck
- Iodine deficiency (most common cause worldwide)
  - Iodine excess can inhibit organification of iodide in abnormal gland
- Drugs (lithium, sulfonamides, amiodarone, interferon alpha)
- **Secondary hypothyroidism**: pituitary dysfunction, postpartum necrosis, neoplasms
- **Tertiary hypothyroidism**: hypothalamic disease
Chronic thyroiditis (Hashimoto’s)

- Most common cause of adult hypothyroidism
  - Up to 10% population increasing with age
  - 7:1 female
- Autoimmune disease
  - Antibodies to thyroglobulin and thyroid peroxidase (TPO)
- Anti-thyroid microsomal antibodies often present
- Rx lifelong synthetic thyroxine (synthroid)
- Monitor TSH

Myxedema

- Extreme lack of T4 and T3
- Boggy eyes and swollen face
- Non-pitting edema
- Delayed deep tendon reflexes
- Decreased CO, enlarged heart
- Pericardial effusion
- Slow mentation
- Somnolence
- Hypothermia

Myxedema Coma

- Life-threatening hypothyroidism
- Obtundation, CO2 retention, coma
- Altered mental status is hallmark
- Can be precipitated by sepsis
- High mortality (30-40%), treat in ICU
- Thyroxine bolus 300mcg, then 100mcg daily
- Hydrocortisone 100mg IV bolus
The Thyroid nodule

- Need to exclude thyroid cancer
  - present in 4.0 to 6.5 percent of thyroid nodules
- Thyroid ultrasound to seek multiple nodules
  - Multiple nodules have same risk of cancer as single
- Check TSH-> low + functioning scan= NOT cancer
- Normal/high TSH or nonfunctional scan
  - Needs Fine Needle Aspiration (FNA)
- Fine Needle Aspiration results / Management
  - Papillary thyroid cancer / thyroidectomy
  - Nuclear atypia / repeat FNA in 3 months
  - Benign / re-evaluate in 1 year

Thyroid Cancer Types

- Papillary most common, least aggressive
- Follicular type often metastasizes
- Anaplastic type (bad!) mainly >60 yo, least common
- Medullary type- C cells, elevated calcitonin, found with MEN syndrome
- Thyroid lymphoma seen in Hashimoto’s

Treatment of Thyroid Cancer

- Total vs near total thyroidectomy
- Lymph node dissection if needed
- Radiation therapy
- Radioactive iodine therapy
- Chemotherapy as an adjunct
- T4 replacement will be needed
Causes of Goiter

- Multinodular goiter most common in elderly
- Iodine-deficiency goiter most common worldwide
- Autoimmune/thyroiditis most common in U.S.
  - Chronic autoimmune (Hashimoto's) thyroiditis
- Subacute thyroiditis
- Toxic goiter
- Graves' disease
- Autonomously functioning thyroid adenoma
- Thyroid cysts
- Thyroid carcinoma

Goiter Clinical Presentation

- Most goiters grow very slowly over many decades
- The majority of patients with goiter are asymptomatic
- Results of thyroid function tests:
  - Low TSH, high T3/T4 -> Graves disease
  - High TSH, positive TPO antibodies -> Hashimotos
- FNA biopsy is indicated if there is a history of rapid growth, pain or tenderness or unusual firmness in one region of the goiter

Hyperthyroidism in Pregnancy

- Occurs in .1 to .4% pregnancies
- Graves' most frequent cause
- Current rec.s say start with β-blocker
  - Next go to thionamide over PTU
- Surgery rarely needed
Parathyroid gland
- Controls calcium homeostasis
- Located posterior poles of thyroid gland
- Calcium sensor in chief cell
- Drop in calcium causes increase PTH
- PTH target organs are bone and kidney

Public domain available at: http://upload.wikimedia.org/wikipedia/commons/7/75/Thyroidgland-intl.png

PTH action to increase calcium
- Increase in bone resorption
- Releases Ca++ and Phosphate to extracellular fluid
- cAMP levels in proximal tubules increases in response to PTH and measurable in urine
- Stimulates Ca++ reabsorption in distal convoluted tubule

PTH action on small intestine
- Indirect effect by activating Vitamin D which stimulates Ca++ reabsorption in the small bowel
- PTH stimulates renal 1alpha-hydroxylase which produces activated Vitamin D
  - Chronic kidney disease inhibits production of Vitamin D
    - Reduces Ca++ reabsorption in the GI tract
    - Hypocalcemia, bone disease and secondary hyperparathyroidism results
    - Treat with Vit D and calcium supplementation
Etiology of Hyperparathyroidism

- Parathyroid adenoma secreting PTH
- High Calcium most commonly detected on routine blood testing while asymptomatic
  - Serum PTH levels will be elevated
  - Familial conditions like MEN-I and -IIa
- Meds: thiazides, lithium, excess Vitamin A
- Hyperthyroidism and acromegaly

Symptoms/Treatment of HyperPTH

- Bones-> osteitis fibrosa cystica
- Abdominal moans-> constipation
- Kidney stones
- Psychic groans-> depression/asthenia
- Rx-> removal of adenoma can be curative
  - Maintain normal Vit D and calcium diet
  - Avoid thiazides and lithium
  - Encourage fluids to avoid kidney stones

Hypoparathyroidism

- Most commonly seen following thyroidectomy, surgical removal parathyroid adenoma
  - Rx-> high doses of Vitamin D and calcium
- Respiratory alkalosis due to hyperventilation
  - Less H+ bound to albumin, so calcium levels drop
  - Low Ca++ lowers the threshold in voltage-gated sodium channels-> tetany
  - Result can be carpopedal spasms
    - Trousseau sign with BP cuff
- Pseudohypoparathyroidism
  - Congenital defect in Ca++ sensor

Vitamin D
(1,25-dihydroxycholecalciferol)

- Obtain vitamin D3 via diet or sunlight
- Converted to active form (1,25) in kidney
  - Catalyzed by 1-alpha hydroxylase
  - Activated by PTH
- Active form binds gut receptors (calbindin)
  - Permits Ca++ absorption
- Chronic renal disease will decrease Vit D
  - Results in secondary hyperparathyroidism

Disorders of Vitamin D
- Recommend 600 units, 800 in elderly
- Screening not recommended
- Rickets is mainly in children
  - Due to low Vit D in diet and/or lack of sun
  - Bones become progressively weaker
- Osteomalacia in adults due to lack of Vitamin D, lack of sun exposure, gastric bypass surgery
- Osteoporosis due to reduced osteoblastic activity
  - Due to lack of estrogen, Vit C, physical activity.

Adrenal Glands
- Adrenal Cortex
  - Three layers:
    - Aldosterone
    - Cortisol
    - Androgens
- Adrenal Medulla
  - Epinephrine 80%
  - Norepinephrine 20%
Glucocorticoids

- **Cortisol** (very potent, accounts for about 95 percent of all glucocorticoid activity)
- **Corticosterone** (provides about 4 percent of total glucocorticoid activity, but much less potent than cortisol)
- **Cortisone** (almost as potent as cortisol)- converted from cortisol and more easily metabolized
- **Prednisone** (synthetic, four times as potent as cortisol)
- **Methylprednisone** (synthetic, five times as potent as cortisol)
- **Dexamethasone** (synthetic, 30 times as potent as cortisol)

### System Glucocorticoid Effects (cortisol)

**Metabolism**
- Degrades muscle protein and increases nitrogen excretion
- Increases gluconeogenesis and plasma glucose levels
- Increases hepatic glycogen synthesis
- Decreases glucose utilization (anti-insulin action)
- Decreases amino acid utilization
- Increases fat mobilization
- Redistributes fat
- Permissive effects on glucagon and catecholamine effects

**Hemodynamic**
- Maintains vascular integrity and reactivity
- Maintains responsiveness to catecholamine pressor effects
- Maintains fluid volume

### Immune function of Cortisol

- Increases anti-inflammatory cytokine production
- Decreases proinflammatory cytokine production
- Decreases inflammation by inhibiting prostaglandin and leukotriene production
- Inhibits bradykinin and serotonin inflammatory effects
- Decreases circulating eosinophil, basophil, and lymphocyte counts (redistribution effect)
- Impairs cell-mediated immunity
- Increases neutrophil, platelet, and red blood cell counts
- Modulates perception and emotion
- Decreases CRH and ACTH release
Four main causes of elevated cortisol

I. Iatrogenic Cushing’s Syndrome (about 25%)
   - Leads to adrenal insufficiency at time of stress
   - Medical emergency
   - Treat with high dose corticosteroids

II. ACTH secreting adenoma of pituitary = Cushing’s Disease (43%)
   - F:M, 8:1

III. Adrenal Adenoma and Carcinoma (10-15%)
IV. Ectopic ACTH from small cell cancer lungs (10-15%)

Cushing’s Effects

- Central obesity
- Hirsutism
- Moon face
- “Buffalo hump”
- Purple striae
- Lanugo hair
- Acne
- Easy bruising
- Supraclavicular fat pads
- Protuberant abdomen
- Thin extremities
- HTN
- Increase infections
Initial Screening

**Overnight Low Dose**
- Administer 1 mg Dexamethasone @ 11pm
- Measure Serum Cortisol @ 8 am
- Serum cortisol < 5 exclude Cushings
- Serum cortisol > 5 (often >10) (+) Cushings

**24 Urine Free Cortisol**
- Values greater than 4 x normal RARE except in Cushing’s
- Good indicator > 125 mg/dL in 24 hours - diagnostic

Next Step in Diagnosis

**Measure ACTH level**
- Low: ACTH being turned off
  - Adrenal tumor or hyperplasia secreting cortisol → negative feedback to pituitary
- High: What is source of ACTH?
  - Pituitary or ectopic source
Next Step in Diagnosis

Measure ACTH level

- Low: ACTH being turned off
  - Adrenal tumor or hyperplasia secreting cortisol → negative feedback to pituitary
- High: What is source of ACTH?
  - Pituitary or ectopic source

What is the source of ACTH?

High dose Dexamethasone Suppression test

- > 50% suppression cortisol → pituitary
  - MRI of pituitary
- < 50% suppression cortisol → ectopic ACTH tumor
  - CT of appropriate region

Treatment of Cushing’s

- Iatrogenic Cushing’s: Taper steroids
- Pituitary Cushing’s: transsphenoidal removal of pituitary adenoma
- Adrenal adenoma or carcinoma: adrenalectomy
Corticoadrenal Insufficiency
“Addison’s disease”

- **Autoimmune destruction**
  - most common cause Addison’s
  - 80% spontaneous cases
- **Infectious diseases — tuberculosis**
  - most common cause worldwide
- **Iatrogenic**
  - B/L adrenalectomy
- **Metastatic**
- **Secondary adrenal insufficiency**
  - abrupt cessation of exogenous steroids
  - pituitary failure

Chronic Adrenal Insufficiency

- **Chronic malaise**
- **Hypotension**
- **Fatigue** that is worsened by exertion and improved with bed rest
- **Weakness** that is generalized, not limited to particular muscle groups
- **Anorexia with nausea and vomiting**
- **Weight loss**
- **Hyperpigmentation**
- **hyperkalemia**

Clinical Features

- **GI symptoms**: anorexia, N/V, vague abdominal pain, wt. loss
- **Mental**: lethargy, confusion, psychosis
- **Hypoglycemia**
- **Hypotension** (orthostatic)
- **Hyperpigmentation** — knuckles, elbows, knees, post. neck, palmar creases, nail beds (primary insufficiency)
- **Other**: irregular or absent menses
Diagnostic Labs

- Serum Na⁺ low (90%)
- Serum K⁺ high (65% primary disease)
- Fasting glucose low
- Low levels of AM cortisol (<3 mcg/dL), high ACTH (> 200 mg/dL) = diagnostic
- Low ACTH = secondary
- Eosinophilia, neutropenia, lymphocytosis

Cosyntropin test (stimulation)

- Give ACTH (cosyntropin - parenterally)
- Measure serum cortisol 30-60 min
- Normal rise to at least 20 mcg/dL
- Less than rise of 20 mcg/dL – suspicious for adrenal insufficiency

Treatment

Hydrocortisone - glucocorticoid
- Prednisone 20-40mg po QD
- Hydrocortisone 50-100mg q6hr IV ("stress" situation)

Fludrocortisone – mineralocorticoid
- Florinef 0.1-0.2mg po QD
- Ensure adequate salt intake
# Pheochromocytoma

- Rare cause of HTN, age 40-60 onset
- Most are due to unilateral medullary tumor
- Bilateral type tends to run in families
- Rule of 10's: 10% bilateral, 10% extra-adrenal, 10% malignant, 10% familial, 10% pediatric, 10% show no HTN
- Palpitations, diaphoresis, and headache
- Picture of refractory or labile HTN

## Presentation and Laboratory Values

- Family Hx of pheochromocytoma or MEN
- First do 24hr urine catecholamines (avoid caffeine, vanilla, fruits)
- False (+): shock, hypoglycemia, stress, clonidine withdrawal, TCAs, and MAOIs
- Clonidine suppression test if above equivocal

## Treatment

- Adrenergic blockade for 3-4 weeks
  - Phenoxybenzamine PO
  - Phentolamine IV
- Surgical laparoscopic adrenalectomy
- Follow up catecholamine testing needed
- Adjunctive radiation and chemotherapy
Control of Aldosterone Synthesis

- Regulated by renin-angiotensin-aldosterone system (RAAS)
- Reduced blood volume triggers formation of renin-> angiotensin-> ACE-> angiotensin II
- Angiotensin II is most powerful stimulus for aldosterone synthesis
- Promotes Na+ reabsorption to restore blood volume to normal

Primary Aldosteronism (Conn’s)

- Aldosterone-producing adenoma
  - Can be surgically removed
- Hypertension
- Hypokalemia
- Muscle weakness due to low K+
- Suppressed renin release
- Rx with aldosterone antagonists
  - spironolactone

Adrenal Androgens

- Dehydroepiandrostone (DHEA)
- Androstenedione
- Testosterone (converted in testes)
- Males make much higher levels of testosterone in testes
- Female androgens mostly derived from DHEA
  - Development of pubic and axillary hair
  - Libido?
Prevalence of Diabetes

- **Total:** 25.8 million children and adults in the United States—6.3% of the population—have diabetes.
- **Diagnosed:** 18.8 million people
- **Undiagnosed:** 7.0 million people
- **Prediabetes:** 79 million people
- **New Cases:** 1.9 million new cases of diabetes were diagnosed in people aged 20 years and older in 2010.

Diabetes consumes 14% of US Health expenditures

- Over 50% related to complications
  - MI
  - CVA
  - End-stage renal disease
  - Retinopathy
  - Foot ulcers
D.M. Diagnostic Criteria

- A1C ≥6.5 percent.
- FPG ≥126 mg/dL
  - Fasting is defined as no caloric intake for at least eight hours. Need to repeat x 1
- Two-hour plasma glucose ≥200 mg/dL during a Glucose Tolerance Test.
- In a patient with classic symptoms of hyperglycemia, a random plasma glucose ≥200 mg/dL.

D.M. Classic Signs & Symptoms

- Polyuria, polydipsia, polyphagia
- Infections
- Weakness
- Lethargy
- Numbness and tingling
- Blurry vision
- Weight loss (mostly type 1)

Risk Factors

- Age (> 45 years old)
- Obesity (BMI>30)
- Sedentary Lifestyle
- Ethnicity (African-American, Hispanic, Asian)
- Family history
- HTN, hypercholesterolemia, high triglycerides
- Gestational diabetes, having a child >9lbs
- Polycystic Ovary Syndrome
Categories of increased risk for diabetes (prediabetes)

- FPG 100 to 125 mg/dL
  - Impaired fasting glucose
- 2-hr PG on the 75-g OGTT 140 to 199 mg/dL
  - Impaired glucose tolerance
- A1C 5.7 to 6.4 percent
  - Prediabetes

Screening Guidelines from ADA

- Asymptomatic individuals should be screened for diabetes if they are overweight (BMI > 25) and have any other additional risk factor(s)
- Beginning at age 45 for those without other risk factors
- Those with normal results and low risk should be re-tested at three-year intervals

Secondary Causes of Hyperglycemia
- Genetic defects
  - Chromosome 12, HNF-1a (formerly MODY3)
  - Chromosome 7, glucokinase (formerly MODY2)
  - Chromosome 20, HNF-4a (formerly MODY2)
  - Type A insulin resistance
- Pancreatitis
- Endocrinopathies
  - Acromegaly
  - Cushing syndrome
  - Glucagonoma
- Drugs: steroids, thiazides, antipsychotics, beta-blockers, niacin, HIV antivirals, oral contraceptives
- Infections
  - Congenital rubella
  - Cytomegalovirus
  - Mumps
- Genetic syndromes associated with diabetes
  - Down syndrome
  - Turner syndrome

Diagnosis of Type 1 Diabetes (DKA)
- Abrupt onset polyuria, polydipsia, polyphagia
- Often present with very high sugars
- Diabetic ketoacidosis (DKA) is a serious consequence
  - DKA occurs in 2% to 5% of patients with type 1 DM/year
  - Most cases occur in already diagnosed type 1 pts.
  - DKA can be the first manifestation of diabetes, esp. in children
  - Precipitated by infection > 50%, also sepsis, MI, and other major concurrent illnesses.
  - Often presents with Kussmaul (deep) respirations, "fruity" breath

DKA Presentation
- Symptoms
  - Nausea/vomiting
  - Thirst/polyuria
  - Abdominal pain
  - Shortness of breath
- Precipitating events
  - Inadequate insulin administration
  - Infection (pneumonia/UTI/gastroenteritis/sepsis)
  - Infarction (cerebral, coronary, mesenteric, peripheral)
  - Drugs (cocaine)
  - Pregnancy
- Physical Findings
  - Tachycardia
  - Dehydration/hypotension
  - Tachypnea/Kussmaul respirations/respiratory distress
  - Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
  - Lethargy/obtundation/cerebral edema/possibly coma
### Tracking DKA Treatment

**Hourly Vital Signs**
- Mental status
- Strict I & O
- Plasma glucose
- Insulin infusion rate
- ABGs/venous pH plus bicarbonate

**Every 2 hours monitor**
- Electrolytes
- Anion gap seen with metabolic acidosis
- EKG: > “u” wave in hypokalemia

---

### DKA Rx

**Volume repletion** is as important as insulin therapy.
- Intravenous 0.9% saline should be started even before the diagnosis is established.
- Subsequent total volume repletion is carried out more slowly at 150 to 500 ml/hr with 0.45% saline
- Switch to 5% glucose-containing solutions once plasma glucose has decreased to 250 until ketoacidosis clears

**Potassium repletion** critical
- Need to r/o hyperkalemia, oliguria or anuria.
- Serious hypokalemia can result as insulin stimulates K+ uptake
- Hypokalemia is the most tragic cause of death (monitor EKG)

---

### Using Insulin in DKA

**Intravenous administration** is far more reliable and results in fewer instances of hypokalemia and hypoglycemia.
- Immediately start insulin drip (bolus had higher risk of cerebral edema)
- Maintain the insulin infusion at 1 to 2 U/hr
- Start 5% glucose if glucose drops below 250 until ketoacidosis clears
- Aim at keeping the plasma glucose level at around 150 mg/dl until the AM
### When to Stop the Insulin Drip?

- Serum anion gap reduced to normal (12 ± 2 meq/L)
- Venous pH is >7.30 or serum HCO₃ is >15 meq/L
- Plasma glucose <200 mg/dL
- Tolerating oral intake

### Hypoglycemia

- Symptoms range from annoying symptoms to confusion, seizures, or coma.
- Severe hypoglycemia can have disastrous consequences
  - particularly if the patient is driving any sort of vehicle
  - working at heights
  - operating potentially dangerous machinery.
- The most common causes are
  - missed meals and snacks
  - insulin dosage errors
  - poor insulin injection technique
  - exercise
  - drugs
  - beta-adrenergic blockers can mask adrenergic symptoms
- Excess alcohol can cause delayed hypoglycemia

### Signs & Symptoms of Hypoglycemia

- Warmth, weakness
- Headache
- Tiredness, drowsiness
- Fainting, dizziness
- Blurred vision
- Mental dullness, confusion
- Abnormal behavior
- Amnesia
- Sweating
- Pallor
- Tachycardia, hypertension
- Palpitations
- Tremor, shaking
- Nervousness, anxiety, irritability
- Tingling, paresthesias (mouth and fingers)
- Hunger, Nausea, vomiting
Hypoglycemic Unawareness

- Up to 25% diabetics (mainly Type 1)
- Loss of warning signs and symptoms
- Progressive loss of glucagon response over 3-5 years
- Epinepherine also loses potency over 10-15 years
- Lowering of glycemic threshold by intensive therapy
- Autonomic neuropathy is also common
  - Gastric dysmotility
  - Gastroparesis causes delayed gastric emptying
  - Diarrhea
  - Orthostatic hypotension
  - Urinary retention
  - Erectile dysfunction is common multifactorial

Hypoglycemia Rx

- Unconscious -> D50 bolus after obtaining glucose for analysis
- Gel form of glucose and simple carbohydrates can be administered by mouth, applying it between the gums and cheeks, from where it slowly and generally safely trickles down into the stomach.
- Glucagon (1 mg administered subcutaneously or intramuscularly) will also usually raise blood glucose levels sufficiently within 15 to 30 minutes, when the patient can then take oral carbohydrates.
  - Glucagon comes in emergency kits and it should always be on hand for patients with a history of severe hypoglycemic episodes.
- Patients with severe hypoglycemia usually respond rapidly to treatment
  - Patients who are postictal or in a prolonged coma may require days to regain normal mental status and cognitive function.
- Quite often, there is amnesia for such extended episodes
- In rare instances, neurologic deficits can be permanent
  - In general, however, long-term consequences of hypoglycemia have not been detected in adults.

Gestational Diabetes Mellitus (GDM)

- Occurs in 6 to 7% of pregnancies in USA
- Risks to the fetus:
  - intrauterine and neonatal mortality
  - respiratory distress syndrome
  - hypoglycemia (need to monitor newborns closely)
  - Macrosomia-> difficult delivery, ?childhood obesity?
- High risk that mom will become diabetic in the future
- Universal screening at 24 to 28 weeks

<table>
<thead>
<tr>
<th>Two hour 75-gram oral glucose tolerance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
</tr>
<tr>
<td>≥92 mg/dL (5.1 mmol/L)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>One-hour</td>
</tr>
<tr>
<td>≥180 mg/dL (10.0 mmol/L)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Two hour</td>
</tr>
<tr>
<td>≥153 mg/dL (8.5 mmol/L)</td>
</tr>
</tbody>
</table>
Treatment of Gestational Diabetes

- Recommend glucoscans 4x daily
  - Upon awakening and 1 hour post prandial
  - Post prandial readings more accurately reflect status

- Treatment with diet: calorie allotment based on ideal body weight

- Insulin when diet not effective
  - Oral agents not approved by the FDA in the U.S

- When to start insulin?
  - ACOG Recommendations:
    - Fasting glucose >95
    - One hour postprandial >130
    - Two hour post prandial >120
  - Monitor with HbA1C
    - Average blood glucose is 20% lower in pregnancy

Chronic Complications of DM

- Microvascular-► intensive control prevents progression
  - Eye disease
    - Retinopathy (Nonproliferative/proliferative)
    - Macular edema
  - Neuropathy
    - Sensory and motor (mono- and polyneuropathy)
    - Autonomic Nephropathy

- Macrovascular-► intensive control ??? benefit
  - Coronary heart disease
  - Peripheral arterial disease
  - Cerebrovascular disease

Diabetic Retinopathy

- Cataracts
- Glaucoma
- Proliferative retinopathy neovascularization, scarring
- Non-Proliferative retinopathy hemorrhages, exudates, microaneurysms, venous dilatation

DM leading cause of Blindness
Diabetic Neuropathy

- **Peripheral neuropathy (LE > UE)**
  - distally symmetric, "stocking glove pattern" loss sensation
- **Autonomic**
  - Gastroparesis, urinary retention, postural hypotension, impotence, fecal incontinence
  - Silent MI

Diabetic Nephropathy

- High glucose levels cause polyuria-renal hyperfiltration
- Chronic hyperfiltration leads to kidney damage
- Proteinuria – early indicator of renal disease
- Rapid progression to dialysis once creatinine reaches 3-4 mg/dl
  - ESRD-DM most common reason for HD

Poor immune function

- Vaginitis
- Periodontitis
- UTI
- Sinusitis
- Otitis externa/ media
- Cellulitis
Complicated Infections

• Gram negative pneumonias
• Infected ulcers
• Gram negative sepsis

![Image](http://commons.wikimedia.org/wiki/File:ULCERCELLULITIS1.JPG)

Public domain available at:
http://commons.wikimedia.org/wiki/File:ULCERCELLULITIS1.JPG

Hyperosmolar Hyperglycemic State (HHS)

• Usually occurs in type 2 elderly
  – osmotic diuresis due to hyperglycemia -> dehydration, insulin secretion suppresses ketosis
• K+ is lost along with Water & Na+
• Severe dehydration
  cardiac perfusion compromise: tachycardia, low Cardiac Output

Diagnostics Criteria:
• Glucose>600 mg/dL
• Serum osm >310
• No acidosis
• No ketones
• Bicarb >15
• Triggers: infection, AMI, pancreatitis, poor compliance

DKA vs. HHS

<table>
<thead>
<tr>
<th></th>
<th>DKA Mild</th>
<th>DKA Moderate</th>
<th>DKA Severe</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25 to 7.30</td>
<td>7.00 to 7.24</td>
<td>&lt;7.00</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15 to 18</td>
<td>10 to &lt;15</td>
<td>&lt;10</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Small</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Small</td>
</tr>
<tr>
<td>Effective serum osmolality (mOsm/kg)²</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Anion gap</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>Variable</td>
</tr>
<tr>
<td>Alteration in sensoria or mental obtundation</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>
**Treatment**

Hyperosmolar Hyperglycemic State

- Saline replacement - (6-10 L)
- Regular Insulin IV (15 units/IV, 15 units SQ)
- Potassium (10 meq to initial fluids)
- Once glucose <250mg/dL – 5% dextrose to fluids

---

**SOMOGYI PHENOMENON**

**DAWN PHENOMENON**

- Somogyi suggested in the 1930s that insulin-induced hypoglycemia when sleeping could cause a pronounced counter regulatory response that subsequently induces hyperglycemia
  - However, patients with morning hyperglycemia typically have high, not low, blood glucose concentrations at night
  - Most common cause of prebreakfast hyperglycemia in patients with type 1 diabetes is hypoinsulinemia
- **Dawn phenomena** - Humans have an increased need for insulin in the early morning due to the early morning release of growth hormone which antagonizes the action of insulin

---

**Diabetic Health Maintenance**

- Smoking cessation counseling Every visit For smokers only.
- Blood pressure Every visit
  - Goal <140/80.
- Dilated eye examination Annually
  - Begin at onset of type 2 diabetes, three to five years after onset of type 1 diabetes.
- Foot examination Annually
  - Every visit if peripheral vascular disease or neuropathy.
Laboratory Studies

- Fasting serum lipid profile Annually
  - May obtain every two years if profile is low risk.
- A1C Every three to six months Goal <7 percent (may be lower or higher in selected patients).
- Urinary albumin-to-creatinine ratio Annually
  - Begin three to five years after onset of type 1 diabetes
  - protein excretion and serum creatinine should also be monitored if persistent albuminuria is present.

Vaccinations

- Pneumococcus One time Patients over age 65
  - need a second dose if vaccine was received 25 years previously and age was <65 at time of vaccination.
- Influenza Annually
- Hepatitis B Three dose series Administer to unvaccinated adults who are ages 19 to 59 years.

Treatment in DM

- Type I: Insulin (basal / bolus)
  - Insulin pumps getting more advanced
- Type II:
  - Diet and Exercise
  - Oral medication should be started at time of diagnosis
    - Metformin preferred
  - Second drug can be added: sulfonurea, incretin class
  - Insulin (if no glycemic control, severe hyperglycemia fasting BG > 240)
    - Start with low dose of long-acting insulin once daily
Tier one: Glucose-lowering Interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Expected glucose-lowering effect</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss, decreased weight</td>
<td>2.0 to 2.0</td>
<td>Broad benefit</td>
<td>Insufficient for most, within first hour</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.0 to 2.0</td>
<td>Metabolic neutral</td>
<td>Less side effects, combination with oral agents possible</td>
</tr>
</tbody>
</table>

Tier two: Additional Considerations

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin type</td>
</tr>
<tr>
<td>Lispro, aspart, glulisine</td>
</tr>
<tr>
<td>Regular</td>
</tr>
<tr>
<td>NPH Insulin glargine</td>
</tr>
<tr>
<td>NPH Insulin detemir</td>
</tr>
<tr>
<td>NPL Insulin degludec</td>
</tr>
</tbody>
</table>

*Extension to beyond 24 hours
Hyperlipidemia Screening

- Screening starts age 25 in high risk males, 35 in females
  - Risk factors include smoking, impaired glucose tolerance
- Normal risk to start at 35 in males, 45 females
- Total cholesterol to HDL ratio best test
  - Can be done non-fasting
- Repeat every three years

Metabolic Syndrome

Need 3 of 5 to diagnose:
- HDL < 40 male, < 50 female
- Elevated BP ≥ 135/85
- Elevated Triglycerides ≥ 150 mg/dL
- Fasting BG 100-125 mg/dL
- Waist Circumference > 35”F, >40”M

Lifestyle risk factors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Treatment of the Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>weight loss program with ultimate goal BMI &lt;25 kg/m²</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>At least 30 min daily</td>
</tr>
<tr>
<td>Atherogenic diet</td>
<td>Reduced intake saturate fat, trans fat, cholesterol</td>
</tr>
</tbody>
</table>

Metabolic risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk*: &lt;100 mg/dL (2.6 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Moderate risk: &lt;130 mg/dL (3.4 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Reduce to at least &lt;140/90</td>
<td></td>
</tr>
<tr>
<td>For IFG, encourage weight reduction and exercise</td>
<td></td>
</tr>
<tr>
<td>For type 2 DM, target A1C &lt;7 percent</td>
<td></td>
</tr>
<tr>
<td>Low dose aspirin for high risk patients</td>
<td></td>
</tr>
</tbody>
</table>
Deciding Whom to Treat…
Cardiovascular Risk Assessment

- Lipid lowering therapy with statins is an intervention that can reduce relative cardiovascular risk by approximately 20 to 30 percent regardless of baseline LDL-C.
- The absolute benefit of treatment will be proportional to the underlying absolute risk.
- Determination of the patient’s underlying CVD risk is the key – rather than aiming to target a specific goal LDL-C.

Risk Factors

- Sex
- Age
- Race
- Total Cholesterol
- HDL Cholesterol
- Systolic Blood Pressure
- Treatment for High Blood Pressure
- Diabetes
- Smoker

American Heart Association

In those without diabetes:
- Treat pts with an estimated 10-year CVD risk ≥7.5.
- If estimated 10-year CVD risk is between 5.0 and 7.5 percent treatment with lower dose is recommended.

In those with diabetes:
- Treat all with at least moderate statin therapy.
- High-intensity statin therapy for those with an estimated 10-year CVD risk ≥7.5.
**Statin Comparable dosing**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>80 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

- To lower LDL 30-35%:

**The 6% Rule:**
- Each doubling of the statin dose usually results in an additional 5% to 7% reduction in LDL-C

**Statin Myopathy**

- Elevated CPK plus myalgias, weakness
  - Can occur at any time while on statin
  - Avoid fibrates, calcium channel blockers, HIV protease inhibitors
- Possible ways to relieve symptoms:
  - Switch to pravastatin or fluvastatin
  - Trial of Co-enzyme Q10
  - Trial of alternate-day dosing
- If unable to tolerate, best to NOT use non-statin therapy (fibrates, niacin slight increase risk)

**CASE 1:**

- 41-year-old woman who has worked at the cosmetics counter of the local department store for many years. Her colleagues in cosmetics noted that her physical appearance had changed—her features had become coarse, her lower jaw was protruding, and her teeth had separated.
- Every night, she had been getting up several times to urinate. Physical examination revealed a woman with coarse facial features, a prominent jaw, and large hands and feet. Her blood pressure was elevated at 170/110. Visual field testing revealed a homonymous hemianopsia.
CASE 2:

• 19-year-old aspiring model who has always dieted to keep her weight in an “acceptable” range. However, within the past 3 months, she has lost 20 lb despite a voracious appetite. She complains of nervousness, sleeplessness, heart palpitations, and irregular menstrual periods. She notes that she is “always hot” and wants the thermostat set lower than her apartment mates.

• On physical examination, she was restless and had a noticeable tremor in her hands. At 5 feet, 8 inches tall, she weighed only 110 lb. Her arterial blood pressure was 160/85, and her heart rate was 110 beats/min. She had a wide-eyed stare, and her lower neck appeared full.
CASE 3

- A 43-year-old elementary school teacher. At her annual checkup, she complained that, despite eating less, she had gained 16 lb in the past year. Her physician might have attributed this weight gain to “getting older” except that she also complained that she has very little energy, always feels cold (when everyone else is hot), is constipated, and has heavy menstrual flow every month. In addition, the physician noticed that her neck was very full.
Thank You!