# Endocrinology

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- Hyperosmolar Nonketotic Hyperglycemic Syndrome
- Hypoglycemia
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## References
**DISORDERS OF GLUCOSE METABOLISM**

**DIABETES MELLITUS (DM)**
- **diagnosis** (confirm with the same test on another day)
  - symptoms of diabetes (polyuria, polydipsia, weight loss, nocturia, polyphagia, blurry vision) PLUS random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) OR
  - FBS ≥ 7.0 mmol/L (126 mg/dL) OR
  - plasma glucose value ≥ 11.1 mmol/L (200 mg/dL) during two hour OGTT
- **diagnostic testing**
  - fasting blood glucose (FBG): best drawn the morning after overnight fast
  - oral glucose tolerance test (OGTT): 75 g glucose ingested, then plasma glucose levels measured following 0 and 120 minutes

**Classification of Diabetes Mellitus (DM)**

<table>
<thead>
<tr>
<th>Table 1. Comparison of Type 1 and Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 Diabetes</strong></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• idiopathic</td>
</tr>
<tr>
<td>• auto-immune</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
</tr>
<tr>
<td>• usually before age 30</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
</tr>
<tr>
<td>• associated with HLA DR3, DR4 and DQ alleles</td>
</tr>
<tr>
<td>• 40% concordance in monozygotic twins</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
</tr>
<tr>
<td>• completely insulin-deficient</td>
</tr>
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<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Risk Factors</strong></td>
</tr>
<tr>
<td>• personal history of autoimmune diseases increases likelihood of developing DM</td>
</tr>
<tr>
<td>• e.g. Graves' disease, myasthenia gravis, Addison's disease, pemphigus anemia</td>
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<td></td>
</tr>
<tr>
<td><strong>Population Prevalence</strong></td>
</tr>
<tr>
<td>• highest in Finland</td>
</tr>
<tr>
<td>• rare in Asian, black, Aboriginal and Hispanic people</td>
</tr>
<tr>
<td><strong>Body Habitus</strong></td>
</tr>
<tr>
<td>• typically normal to wasted</td>
</tr>
<tr>
<td><strong>Pharmacological Therapy</strong></td>
</tr>
<tr>
<td>• insulin required</td>
</tr>
<tr>
<td><strong>Circulating Islet Cell Antibodies</strong></td>
</tr>
<tr>
<td>• 50-85%</td>
</tr>
<tr>
<td><strong>Other Aspects</strong></td>
</tr>
<tr>
<td>• prone to ketoacidosis</td>
</tr>
</tbody>
</table>

**Diabetes Secondary to Specific Etiologies**
- **genetic**
  - Down syndrome, Turner's syndrome, Huntington's disease, genetic defects in β-cell function and insulin action
- **diseases of the endocrine/exocrine pancreas**
  - pancreatitis, neoplasia, cystic fibrosis (CF), hemochromatosis (bronzed diabetes)
- **endocrinopathies**
  - acromegaly, Cushing's syndrome, glucagonoma, hyperthyroidism
- **drug-induced**
  - β-agonists, glucocorticoids, thiazides, phenytoin
- **infections**
  - cytomegalovirus (CMV), congenital rubella

E2 – Endocrinology MCCQE 2002 Review Notes
Gestational Diabetes (GDM) (see Obstetrics Chapter)
- glucose intolerance that develops during pregnancy
- incidence
  - 2-4% of all pregnancies
- risk factors
  - age > 25
  - obesity
  - 1º relative with DM
  - member of high-risk ethnic group
  - previous GDM
  - previous macrosomic baby (> 4 kg)
- screening and diagnosis
  - any pregnant woman should be screened between 24 and 28 weeks
  - 50 g glucose challenge test, measuring glucose one hour later
  - if abnormal (7.8 mmol/L; 140 mg/dL), then 75 g oral glucose tolerance test (OGTT) should be done
  - if any two of the following three values are met or exceeded, a diagnosis of GDM is established
    - fasting glucose ≥ 5.3 mmol/L (95 mg/dL)
    - 1 hr value ≥ 10.6 mmol/L (190 mg/dL)
    - 2 hr ≥ 8.9 mmol/L (160 mg/dL)

Fetus
- maternal hyperglycemia induces hyperinsulinemia in fetus
- results in macrosomia (insulin acts as a growth factor)
- GDM: prone to respiratory distress, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, and prematurity
- preexisting DM: all of the above plus intrauterine growth restriction (IUGR), sacral agenesis, cardiac structural defects

Mother
- increased risk of developing subsequent type 2 DM
- progression of diabetic retinopathy and nephropathy
- management
  - preconception care to normalize HbA1c (if preexisting DM)
  - tight glucose control (shown to decrease both fetal and maternal complications)
  - oral hypoglycemics contraindicated
  - insulin to maintain tight glycemic control if diet inadequate
  - fetus must be monitored carefully

Impaired Glucose Tolerance (IGT)
- diagnosis based on
  - fasting glucose 6.1-6.9 mmol/L (110-125 mg/dL)
  - 2-hour OGTT 7.8-11.1 mmol/L (140-199 mg/dL)
- 1-5% per year develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- associated with progressively greater risk of developing macrovascular complications

COMPLICATIONS OF DIABETES
- the majority of complications involve the vascular system
- aggravating factors: poor glycemic control, inadequate control of hypertension and cholesterol, smoking, high fat diet

Macroangiopathy
- accelerated atherosclerosis leading to coronary artery disease (CAD), stroke, pulmonary vascular disease (PVD)
- most common cause of death in type 2 DM

Microangiopathy
- major chronic complication of type 1 and type 2 DM
- pathognomonic lesion is basement membrane thickening
- classically causes retinopathy, nephropathy and neuropathy
- can involve many other organs, including heart and skin

I. Retinopathy (see Ophthalmology Chapter)
- epidemiology
  - present in 50% of patients after 10 years with DM
  - one of the leading causes of blindness in North America
- types
  - non-proliferative (background)
    - generally no symptoms but may affect macula and impair vision
    - microaneurysms, hard exudates, dot and blot hemorrhages
  - pre-proliferative
    - 10-40% progress to proliferative within one year
    - macular edema, venous shunts and beading, nerve fibre layer microinfarcts (cotton wool spots)
DISORDERS OF GLUCOSE METABOLISM . . . CONT.

- proliferative (see Color Atlas OP13)
  - great risk for loss of vision
  - neovascularization, fibrous scarring, vitreous detachment, retinal detachment

- presentation
  - asymptomatic to complete loss of vision

- prevention and management
  - tight glycemic control
  - photoocoagulation (eliminates neovascularization)
  - vitrectomy
  - frequent follow-up visits with an ophthalmologist (immediate referral after diagnosis of type 2 DM; in type 1, only after 5 years of DM)

2. Nephropathy (see Nephrology Chapter)

- epidemiology
  - diabetes-induced renal failure is the most common cause of renal failure in North America
    - 20-40% of persons with type 1 DM (after 5-10 years) and 4-20% with type 2 DM have progressive nephropathy

- presentation
  - initial changes include microalbuminuria, increased glomerular filtration rate (GFR) (up to 140%), enlarged kidneys
  - over 15 years, progresses to cause hypertension, persistent proteinuria (macroalbuminuria), nephrotic syndrome, renal failure

- prevention and management
  - tight glucose control
  - tight blood pressure control – ACE inhibitors (shown to reduce nephropathic complications) and calcium channel blockers (CCB)
  - limit use of nephrotoxic drugs and dyes
  - protein restriction (controversial)

3. Neuropathy (see Neurology Chapter)

- epidemiology
  - common in both type 1 and type 2 DM

- pathophysiology
  - metabolic defect thought to be due to increased sorbitol and/or decreased myoinositol (exact mechanisms not understood)

- types
  - distal symmetric “glove and stocking” polyneuropathy
  - autonomic dysfunction (e.g. gastroparesis)
  - mononeuropathy (e.g. carpal tunnel syndrome)

- presentation
  - paresthesias or neuropathic pain
  - motor or sensory deficits (including cranial nerves)
  - orthostatic hypotension
  - impotence
  - voiding difficulties
  - foot ulcers

- prevention and management
  - tight glucose control
  - anti-depressants (e.g. amitriptyline), capsaicin, and anti-epileptics (e.g. Tegretol, Neurontin) for painful neuropathic syndromes
  - erythromycin and domperidone for gastroparesis
  - foot care education

4. Other Complications

- skin disease (see Colour Atlas E5)
- bone and joint disease
- cataracts

TREATMENT OF DIABETES

- Diabetes Control and Complications Trial (DCCT) (1993) demonstrated a 50-70% decrease in microvascular complications in type 1 DM in an intensively treated group as compared to a conventionally treated group

- United Kingdom Prospective Diabetes Study (1998) demonstrated a decrease in diabetes complications in intensively treated group compared to conventionally treated group

- marked decrease in vascular complications in those with well-controlled blood pressure
**DISORDERS OF GLUCOSE METABOLISM . . . CONT.**

**Diet**
- energy intake to achieve and maintain desirable weight
- other recommendations as per Canada's Food Guide

**Lifestyle**
- regular physical exercise can improve insulin sensitivity and lower lipid concentrations and blood pressure
- stop smoking and decrease alcohol consumption

**Oral Hypoglycemic Agents** (see Table 2)
- mainly for type 2 DM

**Table 2. Oral Hypoglycemics**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>stimulate release of endogenous insulin</td>
<td>hypoglycemia, nausea, GI discomfort</td>
<td>hepatic or renal impairment</td>
</tr>
<tr>
<td>glyburide (Diabeta)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorpropamide (Diabinase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitimides</td>
<td>stimulate release of endogenous insulin (rapid-acting, better post-prandial glucose control)</td>
<td>hypoglycemia (less frequent than with sulfonylureas)</td>
<td>hypersensitivity, diabetic ketoacidosis (DKA)</td>
</tr>
<tr>
<td>repaglinide (Glucomorm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>reduce gluconeogenesis, increase glucose utilization</td>
<td>lactic acidosis, anorexia, nausea, diarrhea, GI discomfort</td>
<td>hepatic or renal impairment, alcoholism, advanced age</td>
</tr>
<tr>
<td>metformin (Glucophage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>increase peripheral insulin sensitivity, reduce gluconeogenesis</td>
<td>increased TG, weight gain, hepatotoxicity, anemia</td>
<td>liver disease, congestive heart failure (CHF)</td>
</tr>
<tr>
<td>rosiglitazone (Avandia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pioglitazone (Actos)</td>
<td></td>
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</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>decrease the absorption of carbohydrates (thus decreasing postprandial rise of glucose)</td>
<td>flatulence, abdominal cramping, diarrhea</td>
<td>hypersensitivity, DKA, inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td>acarbose (Prandase)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Clinical Pearl**
- Sulfonylureas and Meglitimides “squeeze” endogenous insulin from the pancreas.
- Biguanides and Thiazolidinediones act primarily in peripheral tissues remote from the pancreas.

**Insulin** (see Table 3 and Figure 1)
- doses adjusted for individual patient needs to meet target glycemic control
- administration
  - subcutaneous injections
  - continuous subcutaneous insulin infusion pump
  - IV infusion (regular insulin only)
- preparations
  - ultra-rapid (Humalog)
  - rapid or regular (R or Toronto)
  - intermediate (N or NPH, L or Lente)
  - long-acting (U or Ultralente)
- multiple daily injections of different types of insulin usually necessary for optimal glucose control
- estimate of total daily insulin requirement when starting an adult type 1 diabetes patient on insulin = 0.5 - 0.6 units/kg

**Table 3. Kinetics of Different Insulins**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Duration</th>
<th>Onset (hours)</th>
<th>Peak (hours)</th>
<th>Usual Effective Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humalog (H)</td>
<td>very short</td>
<td>5-10 min</td>
<td>30-40 min</td>
<td>2-3</td>
</tr>
<tr>
<td>Regular (R)</td>
<td>short</td>
<td>1/2-1</td>
<td>1-3</td>
<td>5-7 (dose-dependent; may be longer)</td>
</tr>
<tr>
<td>NPH/lente (N)</td>
<td>intermediate</td>
<td>2-4</td>
<td>6-10</td>
<td>14-18</td>
</tr>
<tr>
<td>Ultralente</td>
<td>long</td>
<td>4-5</td>
<td>—</td>
<td>18-28</td>
</tr>
</tbody>
</table>
Glucose Monitoring
- frequent self-monitoring and recording of blood glucose is now standard management
- hemoglobin A1c (HbA1c or glycosylated hemoglobin)
  - percentage indicates level of plasma glucose over past 3 months
  - extremely useful for monitoring patient's long-term diabetes control
  - goal is to maintain HbA1c within 5-8% range (i.e. average blood glucose 5.0-11.0 mmol/L)
  - HbA1c ≥ 10% indicates poor control

Variable Insulin Dose Schedule (“Sliding Scale”)
- patient takes fixed doses of intermediate-acting insulin (N) but varies doses of fast-acting insulin (R or H) based on blood glucose reading at time of dose
- use baseline R or H dose when in blood glucose target range; add or subtract units when above or below target
- allows patient to make corrections to avoid long periods of hyper- or hypoglycemia

Table 4. Sample Insulin Sliding Scale for Regimen of 3 Daily Injections

<table>
<thead>
<tr>
<th>Blood Glucose (mmol/L)</th>
<th>Breakfast</th>
<th>Insulin (number of units)</th>
<th>Supper</th>
<th>Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R or H</td>
<td>N</td>
<td>R or H</td>
<td>N</td>
</tr>
<tr>
<td>&lt; 3.0</td>
<td>-2</td>
<td>25</td>
<td>-2</td>
<td>18</td>
</tr>
<tr>
<td>3.1-3.9</td>
<td>-1</td>
<td></td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>target range: 4.0-8.0</td>
<td>12</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>8.1-12.0</td>
<td>+1</td>
<td></td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>12.1-17.0</td>
<td>+2</td>
<td></td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>&gt; 17.0</td>
<td>+3</td>
<td></td>
<td>+3</td>
<td></td>
</tr>
</tbody>
</table>

Insulin Pump Therapy
- external, battery-operated pump continuously delivers basal dose of fast-acting insulin through small subcutaneous catheter
- at meals, patient programs pump to deliver extra insulin bolus
- basal dose may be increased or decreased based on activity, sleep, etc.
- advantages: more flexible lifestyle (sleep in, eat / skip meals when desired), better glucose control
- disadvantages: very expensive, increased risk of DKA if pump inadvertently disconnected, frequent blood glucose testing required

DIABETIC KETOACIDOSIS (DKA)

Pathophysiology
- insulin deficiency combined with increased counter-regulatory hormones i.e. glucagon, cortisol, growth hormone (GH), catecholamines
- clinically involves two factors: lack of insulin (non-compliance, inadequate dose, initial presentation of DM) and/or precipitant (surgery, infection, emotional stress)
- unrestricted hepatic glucose production → extreme hyperglycemia
- lipolysis → free fatty acids (FFA) → ketoacids → acidosis
- osmotic diuresis causes dehydration and electrolyte abnormalities
DISORDERS OF GLUCOSE METABOLISM . . . CONT.

Clinical Features
- typical patient: young type 1 DM
- presentation preceded by polyuria and polydipsia
- level of consciousness (LOC) may be decreased with high serum osmolality (> 330 mOsm/kg)
- dehydration and ketoacidosis
  - anorexia, nausea, vomiting, fatigue
  - abdominal pain (especially in children)
  - fruity-smelling breath (due to acetone)
  - Kussmaul's respirations (rapid deep breathing)

Investigations and Laboratory Findings
- increased blood glucose (BG) (11 mmol/L to > 55 mmol/L), decreased Na, decreased HCO₃, increased BUN
- also measure K⁺, urine glucose and ketones
- hyperglycemia and ketonemia
  - ketones in range of 15 mmol/L
- wide anion gap metabolic acidosis (pH ≤ 7.3 and/or HCO₃ ≤ 15) plus possible secondary respiratory alkalosis due to Kussmaul's respirations; can also have metabolic alkalosis from vomiting and dehydration

Treatment
- rapid diagnosis and close medical supervision are essential
- in general, monitor degree of ketoacidosis with anion gap, not blood glucose or ketone level
- rehydration
  - critical in order to maintain adequate cardiac output and renal function
  - bolus of NS initially followed by high rate NS infusion
  - ~ 400 mEq Na⁺ is lost in the urine (osmotic diuresis, buffering of ketone acid anions, hyperglucagonemia and hypoinsulinemia leading to direct renal excretion)
- insulin
  - initial bolus of 5-10 U (or 0.1 U/kg) IV in adults followed by continuous infusion at 5-10 U (or 0.1 U/kg) per hour
  - when blood glucose ≤ 15 mmol/L (270 mg/dL) add D5W
- potassium
  - avoid hypokalemia
  - K⁺ lost from cells due to insulin deficiency and general catabolic state
  - blood levels do not reflect total body losses which may be 400-500 mEq
  - K⁺ falls during treatment due to rehydration and insulin action (drives K⁺ into cells)
  - normal or low K⁺ level initially indicates severe deficiency and requires cardiac monitoring
  - replace as KCl
- bicarbonate
  - avoid giving unless life-threatening situation and/or shock
- treatment of precipitating cause with patient education to prevent further episodes of DKA
- treat cerebral edema with mannitol

Prognosis
- 2-5% mortality in developed countries
- serious morbidity and mortality often result from
  - sepsis
  - pulmonary and cardiovascular complications
  - thromboembolic complications
  - cerebral edema

HYPEROSMOLAR NONKETOTIC HYPERGLYCEMIC SYNDROME

Pathophysiology
- usually complication of type 2 DM
- profound dehydration resulting from hyperglycemia
- precipitating events: infection, stroke, myocardial infarction, trauma, drugs (glucocorticoids, immunosuppressives, diuretics), medical procedures (dialysis), burns
- reduced fluid intake, especially in elderly, bedridden patients

Clinical Features
- extreme hyperglycemia, hyperosmolarity, volume depletion and CNS signs

Investigations and Lab Findings
- high urine glucose, negative or low ketones
- BG often > 55 mmol/L (1,000 mg/dL), but not a good indicator of severity
- urine negative for ketones; blood ketones reflect only starvation ketosis
- high serum osmolality
- electrolytes may show spurious hyponatremia (decrease in 3 mEq/L Na⁺ for every 10 mmol/L 180 mg/dL) increase in glucose
- nonketotic mixed metabolic acidosis may be present due to other acute underlying conditions (sepsis, renal failure, lactic acidosis)
DISORDERS OF GLUCOSE METABOLISM . . . CONT.

**Treatment**
- rehydration with NS to restore intravascular volume, then 1/2 NS
- identify and treat precipitating cause(s)
- insulin (0.1 U/kg/hour) may or may not be necessary
- cerebral edema may result if osmolality is treated too aggressively
- overall mortality high (> 50%)

**HYPOGLYCEMIA**

**Definition (Whipple's Triad)**
- serum glucose below a certain level (see below) PLUS
  - neuroglycopenic symptoms OR
  - adrenergic symptoms (autonomic response) PLUS
  - relief provided by administration of glucose
- serum glucose at onset of symptoms
  - < 2.5 mmol/L (45 mg/dL) in male patients
  - < 2.2 mmol/L (40 mg/dL) in female patients
- occurs most often in insulin-treated diabetics, usually due to problems with matching insulin dose to estimated blood glucose levels

**Clinical Features of Hypoglycemia**
- adrenergic symptoms (typically occur first)
  - palpitations, sweating, anxiety, tremor, tachycardia, hunger
- neuroglycopenic symptoms
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

**Types of Hypoglycemia**

1. **Postprandial (Reactive) Hypoglycemia**
   - occurs 1.5-6 hours after a meal and recovers spontaneously
   - manifested primarily as adrenergic symptoms due to autonomic discharge
   - thought to be over-diagnosed and over-treated
   - etiology
     - alimentary hyperinsulinism
     - post-GI surgery (gastrectomy, pyloroplasty, vagotomy)
     - may also be induced by galactosemia and fructose intolerance
   - treatment
     - frequent, small feeds
     - weight loss

2. **Fasting Hypoglycemia**
   - imbalance between production of glucose by liver and utilization in peripheral tissues
   - etiology
     - defective gluconeogenesis with inability to maintain glucose concentration if food is withheld
     - hormone deficiencies (hypopituitarism, adrenal insufficiency, inadequate catecholamines or glucagon)
     - enzyme defects
     - substrate deficiency
     - liver disease (cirrhosis, uremia)
     - drugs (ethanol, propranolol, salicylates)
     - excessive utilization of glucose
     - hyperinsulinism (insulinoma, sulfonylurea, exogenous insulin, sepsis)
     - appropriate insulin levels (extrapancreatic tumours)
   - treat underlying cause

**SYNDROME X - INSULIN RESISTANCE SYNDROME**
- postulated syndrome related to insulin resistance
  - association between hyperglycemia, hyperinsulinemia, hypertension, central obesity, and dyslipidemia (elevated LDL, VLDL and TG and reduced HDL)
- obesity aggravates extent of insulin resistance
- complications include atherosclerosis, coronary artery disease (CAD), stroke and MI
DYSLIPIDEMIAS

- metabolic disorders characterized by elevations of fasting plasma cholesterol and/or triglycerides (TG), and/or low HDL

LIPOPROTEINS
- consist of a lipid core that is surrounded by a shell of water-soluble proteins and phospholipids
- transport lipids within the body

Table 5. Lipoprotein Physiology

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exogenous Pathway</strong></td>
<td></td>
</tr>
<tr>
<td>Chylomicron</td>
<td>transports dietary triglycerides from gut to adipose tissue and muscle</td>
</tr>
<tr>
<td><strong>Endogenous Pathway</strong></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>transports hepatic-synthesized TG from liver to adipose tissue and muscle</td>
</tr>
<tr>
<td>LDL</td>
<td>transports cholesterol from liver to peripheral tissues</td>
</tr>
<tr>
<td>HDL</td>
<td>transports cholesterol from peripheral tissues to liver; acts as reservoir for apolipoproteins</td>
</tr>
</tbody>
</table>

Table 6. Abnormal Lipid Values in mmol/L (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>3.4-4.1 (130-160)</td>
<td>2.3-4.0 (90-155)</td>
<td>0.6-0.95 (23-37)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.1-4.9 (160-190)</td>
<td>4.0-10.0 (155-385)</td>
<td>-</td>
</tr>
<tr>
<td>Marked</td>
<td>&gt; 4.9 (190)</td>
<td>&gt; 10.0 (385)</td>
<td>&lt; 0.6 (23)</td>
</tr>
</tbody>
</table>

Figure 2. Lipid Pathways
Illustration by Glen Oomen
**Table 7. Hyperlipidemias**

<table>
<thead>
<tr>
<th>Hyperlipidemia</th>
<th>Lipoproteins</th>
<th>Lipid Abnormalities</th>
<th>Defect</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypercholesterolemias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Familial Hypercholesterolemia</td>
<td>IIA</td>
<td>111 –</td>
<td>• defective or absent LDL receptors</td>
<td>• homozygotes: manifest CAD and other vascular disease in childhood and die young (&lt; 20 yrs.) if untreated</td>
</tr>
<tr>
<td>• autosomal dominant</td>
<td></td>
<td></td>
<td></td>
<td>• heterozygotes: develop CAD, 50% chance of MI by age 30 in men</td>
</tr>
<tr>
<td>b) Polygenic Hypercholesterolemia</td>
<td>IIA</td>
<td>11 –</td>
<td>• few mild inherited defects in cholesterol metabolism</td>
<td>• tendonous xanthomata, xanthelasmas, corneal arcus</td>
</tr>
<tr>
<td>(most common)</td>
<td></td>
<td></td>
<td></td>
<td>• asymptomatic until vascular disease develops</td>
</tr>
<tr>
<td>2. Hypertriglyceridemias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Familial Hypertriglyceridemia</td>
<td>IV</td>
<td>1111</td>
<td>• excessive hepatic TG synthesis</td>
<td>• risk premature atherosclerosis</td>
</tr>
<tr>
<td>b) Familial Lipoprotein Lipase Deficiency</td>
<td>I, V</td>
<td>11 –</td>
<td>• defective or absent lipoprotein lipase</td>
<td>• expressed in early adulthood, triad of obesity, hypertriglyceridemia, and hyperinsulinemia (also hyperuricemia)</td>
</tr>
<tr>
<td>3. Combined Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Familial Combined Hyperlipidemia</td>
<td>IIIb</td>
<td>1111</td>
<td>• excessive hepatic synthesis of apolipoprotein B</td>
<td>• CAD and other vascular problems but otherwise asymptomatic</td>
</tr>
<tr>
<td>b) Dysbetalipoproteinemia</td>
<td>III</td>
<td>1111</td>
<td>• abnormal apoprotein E</td>
<td>• palmar or tuberous xanthomata seen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• can be well until vascular disease develops</td>
</tr>
</tbody>
</table>

**SECONDARY CAUSES OF HYPERLIPIDEMIAS**

1. Hypercholesterolemia
   - diet
   - hypothyroidism
   - renal disease (nephrotic syndrome)
   - liver disease (cholestatic)
   - drugs (cyclosporine)
   - diabetes
   - paraproteinemia

2. Hypertriglyceridemia
   - obesity
   - alcohol
   - drugs (β-blockers without intrinsic sympathetic activity (ISA) birth control pill, hydrochlorothiazide, retinoic acid, glucocorticoid)
   - renal disease (uremia)
   - liver disease (acute hepatitis)

**APPROACH TO DYSLIPIDEMIAS**

- establish presence of coronary artery disease (CAD), peripheral vascular disease (PVD), cerebrovascular disease (CVD) risk factors outlined below for purpose of risk stratification

**History Suggestive of Primary Dyslipidemia**

- marked hyperlipidemia
- personal and/or family history of premature CAD < 40 yrs and resistance to conventional therapy
- tendon xanthomata, xanthelasma, eruptive xanthomata, lipemia retinalis, arcus in young person

**Screening and Investigation**

- increased LDL cholesterol is a major risk factor for atherosclerosis, especially CAD
- lowering LDL cholesterol associated with decreased CVD risk, and decreased total mortality
- increased HDL associated with decreased CVD risk
DYSLIPIDEMIAS . . . CONT.

- Hypertriglyceridemia is an independent risk factor for CAD in people with diabetes and postmenopausal women
- Screening recommended for those with
  - CAD
  - Family history of hyperlipidemia or premature CAD
  - Other risk factors (e.g., hypertension, renal failure, obesity, smokers, diabetes)
- Good evidence for both primary and secondary intervention

**Risk Factors for CAD** (see Cardiology Chapter)
- Modified from National Cholesterol Education Program (NCEP)
- Positive risk factors
  - Age: males > 45; females > 55, or premature menopause without hormone replacement therapy
  - Family history of CAD: MI or sudden death < age 55 in father or other first-degree male relative, or < age 65 in mother or other first-degree female relative
  - Current smoker
  - Hypertension (BP > 140/90) or on anti-hypertensive medications
  - Low HDL-cholesterol (< 0.90 mmol/L; 35 mg/dL)
  - DM or impaired glucose tolerance (IGT)
  - Hypertriglyceridemia (> 2.3 mmol/L; 90 mg/dL)
  - Abdominal obesity (BMI ≥ 27; waist:hip ≥ 0.9 in M, ≥ 0.8 in F)
- Negative risk factors
  - High HDL-cholesterol

**Table 8. Risk Stratification for CAD in Individuals with Elevated LDL**

<table>
<thead>
<tr>
<th>CAD Risk Classification</th>
<th>% over 10 years</th>
<th>Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>&gt; 40%</td>
<td>Clinical macrovascular disease</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 20%</td>
<td>Males &gt; 35, postmenopausal females, &gt; 3 risk factors or marked hyperlipidemia with no clinical macrovascular disease</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10-20%</td>
<td>Males &gt; 35, postmenopausal females, 2-3 risk factors with no clinical macrovascular disease</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 10%</td>
<td>Males &lt; 35, postmenopausal females, &lt; 2 other risk factors</td>
</tr>
</tbody>
</table>

**TREATMENT OF DYSLIPIDEMIAS**

- For clinical guidelines, see Fodor et al., (2000) in the References section
- For anti-lipidemic agents, see the Common Medications section

**Hypercholesterolemia**

- Conservative for 4-6 months
  - Phase I diet
    - < 30% calories from fat with < 10% saturated
    - < 300 mg cholesterol/day
  - Smoking cessation
  - Limit alcohol consumption to ≤ 2 drinks/day (especially if elevated TG)
  - Aerobic exercise (especially if obese, type 2 DM)
    - E.g. 30-60 minute brisk walk for 4-7 days/week
  - Weight loss (especially if BMI > 25, waist circumference > 90 cm for F or > 100 cm for M)
  - Change medications where appropriate
  - Treat secondary causes
  - Hormone replacement therapy (HRT)

**Table 9. Initiation and Target LDL Level in mmol/L (mg/dL) by Risk Group**

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Target LDL</th>
<th>Target Total/HDL</th>
<th>Target TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>&lt; 2.5 (100)</td>
<td>&lt; 4.0 (155)</td>
<td>&lt; 2.0 (75)</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 3.0 (115)</td>
<td>&lt; 5.0 (195)</td>
<td>&lt; 2.0 (75)</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 4.0 (155)</td>
<td>&lt; 6.0 (230)</td>
<td>&lt; 2.0 (75)</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 5.0 (195)</td>
<td>&lt; 7.0 (270)</td>
<td>&lt; 3.0 (115)</td>
</tr>
</tbody>
</table>
DYSLIPIDEMIAS . . . CONT.

Hypertriglyceridemia
- conservative measures usually effective; treat after 4-6 months if
  - TG > 10 mmol/L (385 mg/dL) - to prevent pancreatitis
  - mild-moderate elevated TG when
    - very high CAD risk
    - high risk (> 3 RFs)
    - diabetes
    - associated low HDL plus other risk factors
    - combined hyperlipidemia

Isolated Low HDL
- no evidence supporting treatment
- can justify treatment if very high-risk patient or family history of premature CAD

Follow-Up
- every 4-6 months for lipid profiles and LFTs
- check CK baseline and again if patient complains of myalgia
- increase dose and add second agent to achieve target goals

OBESITY

Definitions
- 20% or greater above ideal body weight (IBW) (Met. Life Ins. tables); 170% of IBW or BMI > 40 is morbid obesity
- most practical index is BMI (body mass index) = weight/height² (kg/m²)
  - BMI < 20 or > 27 leads to increased health risk

Epidemiology
- 15-25% of North American adults

Possible Risk Factors
- increasing age
- genetic - variations in energy expenditure
- behaviour/lifestyle - diet and exercise
- secondary causes
  - endocrine: e.g. Cushing's syndrome, polycystic ovarian disease (PCOD)
  - drugs: e.g. antidepressants, antiepileptics and antipsychotics
  - hypothalamic injury: trauma, surgical, lesions in ventromedial or paraventricular median nucleus

Pathophysiology
- positive energy balance: energy input > energy output

Complications
- cardiovascular
  - hypertension, CAD, CHF, varicose veins, sudden death from arrhythmia
- respiratory
  - dyspnea, sleep apnea, pulmonary embolus, infections
- gastrointestinal
  - gallbladder disease, gastroesophageal reflux disease (GERD), fatty liver
- musculoskeletal
  - osteoarthritis
- endocrine/metabolic
  - impaired glucose tolerance (IGT) to type 2 DM, hyperuricemia, hyperlipidemia
  - PCOD, hirsutism, irregular menses, infertility
- increased risk of neoplastic diseases
  - endometrial, post-menopausal breast, prostate, colorectal cancers

Treatment
- general recommendations
  - treatment should be based on medical risk
  - safest and best therapy is a comprehensive approach including caloric restriction, increased physical activity and behaviour modification
- diet
  - caloric restriction with a balanced diet with reduced fat, sugar and alcohol
- exercise
- behaviour modification
  - individual or group therapy
  - self-monitoring, stimulus control, stress management, cognitive change, crisis intervention
- drug therapy
  - serotonergic-appetite suppressants fenfluramine-phentermine (Fen-Phen) were found to cause valvular heart disease and primary pulmonary hypertension (withdrawn)
  - pancreatic lipase inhibitor: orlistat (Xenical) found to be mildly to moderately effective
- surgical therapy
  - gastroplasty (“stomach stapling”) is treatment of last resort (controversial)
  - liposuction
    - weight loss is regained by fat accumulation at the same site or elsewhere
    - not advocated if patient has significant medical comorbidities
PITUITARY GLAND

Hypothalamic Control of Pituitary
- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

Anterior Pituitary Hormones
- growth hormone (GH), leutenizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticopin hormone (ACTH), prolactin (PRL)

Posterior Pituitary (Hypothalamic) Hormones
- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- stored in and released from the posterior pituitary

Table 10. The Pituitary Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRL</td>
<td>• dopamine&lt;br&gt;• D2-receptor agonists (bromocriptine)</td>
<td>• dopamine antagonists&lt;br&gt;• thyroid releasing hormone (TRH)</td>
</tr>
<tr>
<td>ACTH</td>
<td>• dexamethasone&lt;br&gt;• cortisol</td>
<td>• cortisol releasing hormone (CRH)&lt;br&gt;• metyrapone (11-ß-hydroxylase inhibitor)&lt;br&gt;• insulin-induced hypoglycemia&lt;br&gt;• fever, pain</td>
</tr>
<tr>
<td>TSH</td>
<td>• circulating thyroid hormones</td>
<td>• TRH</td>
</tr>
<tr>
<td>GH</td>
<td>• glucose challenge&lt;br&gt;• somatostatin&lt;br&gt;• dopamine agonists&lt;br&gt;• insulin like growth factor (IGF)-1</td>
<td>• insulin-induced hypoglycemia&lt;br&gt;• exercise, REM sleep&lt;br&gt;• arginine, clonidine, propranolol, L-dopa&lt;br&gt;• growth hormone releasing hormone (GHRH)</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>• estrogen&lt;br&gt;• testosterone&lt;br&gt;• continuous GnRH infusion</td>
<td>• GnRH in boluses</td>
</tr>
<tr>
<td>ADH</td>
<td>• decreased serum osmolality</td>
<td>• increased serum osmolality&lt;br&gt;• hypovolemia&lt;br&gt;• stress, fever, pain</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>• EtOH</td>
<td>• suckling&lt;br&gt;• distention of female genital tract</td>
</tr>
</tbody>
</table>

GROWTH HORMONE (GH)
- polypeptide, secreted in bursts

Physiology
- serum GH undetectable much of the day, suppressed after meals that are high in glucose content, sustained rise during sleep
- necessary for normal linear growth
- acts indirectly through serum factors synthesized in liver
  - insulin-like growth factors (IGF)
  - previously known as “somatomedins”
- IGF shares some insulin-like actions and thus stimulates growth of bone and cartilage

Regulation
- stimulated by GHRH, sleep, exercise, insulin, hypoglycemia, arginine, L-dopa, propranolol, clonidine
- inhibited by somatostatin, glucocorticoids, hyperglycemia, hypothyroidism
- “long loop” negative feedback by IGF-1 (somatomedin C)

Pathology
- decreased GH
  - not very significant in adults but important in children (see Pediatrics Chapter)
  - treatment: recombinant human growth hormone

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PITUITARY GLAND . . . CONT.

- increased GH
  - hypersecretion causes gigantism in children, acromegaly in adults
  - clinically seen as thickened soft tissues (palms, heels), sweating, large bones, coarse features, diabetes, carpal tunnel syndrome, osteoarthritis, hypertension, and increased risk of colon cancer
  - definitive diagnosis: increase in GH with oral glucose tolerance test (OGTT)
  - causes
    - pituitary adenomas most common
    - occasionally pituitary adenoma produces both prolactin and GH
    - rarely carcinoid tumours and pancreatic islet tumours make GHRH
  - treatment: surgery, radiation, bromocriptine (dopamine agonist), octreotide (somatostatin analogue)

PROLACTIN (PRL)
- polypeptide

Physiology
- promotes milk production
- antagonizes sex steroids peripherally

Regulation
- stimulation
  - physiologic: sleep, stress, pregnancy, hypoglycemia, mid-menstrual cycle, breast feeding, TRH, sexual activity
  - pharmacologic: psychotropics (e.g. haloperidol, risperidone), antihypertensives (e.g. reserpine, verapamil), α-methyl dopa, opiates, high-dose estrogens, metoclopramide, domperidone, cimetidine
  - pathologic
    - various hypothalamic-pituitary causes (e.g. pituitary microadenoma, pituitary stalk transection)
    - primary hypothyroidism (increased TRH)
    - chronic renal failure (secondary to reduced clearance)
    - liver cirrhosis
- inhibition
  - physiologic: tonic inhibition by dopamine
  - pharmacologic: dopamine agonists (e.g. bromocriptine)

Pathology
- hypoprolactinemia
  - inability to lactate
  - may be the first sign of Sheehan’s syndrome (postpartum pituitary hemorrhage) (see Obstetrics Chapter)
- hyperprolactinemia
  - galactorrhea, infertility, hypogonadism (women and men)
  - serum prolactin levels > 300 µg/L (300 ng/mL) virtually diagnostic of prolactinoma
  - prolactin-secreting tumours may be induced by estrogens and may grow during pregnancy
  - treatment includes bromocriptine or cabergoline (long-acting dopamine agonist), surgery +/- radiation
  - these tumours are very slow-growing and sometimes require no treatment

LEUTINIZING HORMONE (LH) AND FOLLICLE STIMULATING HORMONE (FSH)
- glycoproteins with same α subunit as TSH and hCG
- possibly secreted by the same cells (gonadotrophs)

Physiology
- both released in pulsatile fashion, but FSH has a longer half-life (3-4 hours vs. 50 minutes for LH) and thus fluctuates less throughout the day
- gonadotropins: stimulate gonads (ovaries and testicles) via cAMP
- in the ovary
  - LH stimulates ovarian theca cells to produce androgens (which are subsequently converted to estrogens in granulosa cells) and induces luteinization in ovarian follicles
  - FSH stimulates growth of granulosa cells in ovarian follicle and controls estrogen formation
- in the testis
  - LH controls testicular production of testosterone in Leydig cells
  - FSH, together with intra-testicular testosterone, stimulates Sertoli cells tubules to produce sperm

Regulation
- GnRH stimulates both FSH and LH
- inhibition
  - female: estrogen and progesterone
  - male: testosterone and inhibin
**PITUITARY GLAND**

**Pathology**
- secondary hypersecretion in gonadal failure
- decreased gonadotropins (see Gynecology Chapter)
  - hypogonadism
  - amenorrhea
  - impotence
  - loss of body hair
  - fine skin
  - testicular atrophy
  - failure of pubertal development
  - treated with Pergonal and hCG, or LHRH analogue if fertility desired; otherwise treat with estrogen/testosterone

**ANTIDIURETIC HORMONE (ADH)**
- octapeptide synthesized in supraoptic nuclei of hypothalamus and secreted down pituitary stalk to posterior lobe of pituitary
- also known as “vasopressin”

**Physiology**
- major action is via cAMP in renal collecting ducts; alters permeability of membrane to water
- allows reabsorption of water thereby increasing urine concentration

**Regulation**
- major secretory stimulus is serum osmotic pressure detected by osmoreceptors in hypothalamus
- hypovolemia, stress, fever, pain may also stimulate ADH
- contracted plasma volume is a more potent stimulator of water retention than osmolality change (mediated through renin-angiotensin system)

**Pathology**

1. **Diabetes Insipidus (DI)** (see Nephrology Chapter)
   - definition: passage of large volumes of dilute urine
   - central vs. nephrogenic
     - central DI: insufficient ADH due to dysfunction of hypothalamic nuclei (e.g. tumours, hydrocephalus, histiocytosis, trauma)
     - nephrogenic DI: collecting tubules in kidneys resistant to ADH (e.g. drugs including lithium, hypercalcemia, hypokalemia)
     - psychogenic polydipsia must be ruled out
   - diagnosis
     - fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI
     - response to exogenous ADH will distinguish central from nephrogenic DI
   - treatment
     - DDAVP (vasopressin) for total DI
     - DDAVP or chlorpropamide, clofibrate, carbamazepine for partial DI
     - nephrogenic DI treated with solute restriction and thiazides

2. **Syndrome of Inappropriate ADH secretion (SIADH)**
   - ADH excess associated with hyponatremia without edema; must rule out other causes of excess ADH e.g. hypovolemic (adrenocortical insufficiency), edematous (hypothyroidism), and hypertensive (renovascular stenosis) states
   - causes
     - malignancy (lung, pancreas, lymphoma)
     - CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
     - chest disease (TB, pneumonia, empyema)
     - drugs (vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine)
     - stress (post-surgical)
   - diagnosis
     - euvolemic hyponatremia with inappropriately concentrated urine
     - normal thyroid, adrenal and renal functions
   - treatment
     - treat underlying cause, fluid restriction, demeclocycline (antibiotic with anti-ADH effects)

**OXYTOCIN** (see Obstetrics and Gynecology Chapters)
- a nonapeptide synthesized in paraventricular nuclei and supraoptic nuclei of hypothalamus and stored in posterior pituitary

**Physiology**
- causes uterine contractions but physiologic role in initiating labour unclear
- as impairment of oxytocin production does not interfere with normal labour

**Regulation**
- secretion stimulated by suckling and distention of the female genital tract
- secretion inhibited by ethanol
PITUITARY GLAND . . . CONT.

PITUITARY PATHOLOGY

Pituitary Adenoma (see Colour Atlas NS18)
- related to size and location
  - visual field defects (usually bitemporal hemianopsia), oculomotor palsies, increased ICP (may have headaches)
  - skull radiograph: “double floor” (large sella or erosion), calcification
  - CT and MRI far more sensitive for diagnosis
- related to destruction of gland
  - hypopituitarism
- related to increased hormone secretion
  - PRL
    - prolactinoma is most common pituitary tumour
    - galactorrhea
  - GH
    - acromegaly in adults (see Colour Atlas E4), gigantism in children
  - ACTH
    - Cushing's disease = Cushing's syndrome caused by a pituitary tumour
    - tumours secreting LH, FSH and TSH are rare

Craniopharyngioma (see Pediatrics Chapter)

Empty Sella Syndrome
- sella turcica appears enlarged on x-ray because pituitary gland is distorted
- generally euvituitar - no treatment necessary

Pituitary Apoplexy
- acute hemorrhage/infarction of pituitary tumour
- sudden severe headache
- altered LOC
- ocular symptoms
- note: ophthalmoplegia with pituitary tumour likely indicates apoplexy
  - since tumour rarely gets big enough to encroach on cranial nerves
- neurosurgical emergency: acute decompression of pituitary via trans-sphenoidal route

Clinical Pearl
GH, LH, FSH, TSH, ACTH, PRL
- A compressive adenoma in the pituitary will impair hormone production in this order
  (i.e. GH-secreting cells are most sensitive to compression)
- Mnemonic: “Go Look For The Adenoma Please”

HYPOPITUITARISM

Etiology
- Mnemonic: eight “I”s
  - Invasive: generally primary tumours
  - Infarction: e.g. Sheehan's syndrome
  - Infiltrative disease e.g. sarcoidosis, hemochromatosis, histiocytosis
  - Iatrogenic: following surgery or radiation
  - Infectious: e.g. syphilis, TB
  - Injury: severe head trauma
  - Immunologic: autoimmune destruction
  - Idiopathic: familial forms, congenital midline defects

Clinical Features
- typical clinical progression in panhypopituitarism
  - fall in GH, clinically not apparent
  - fall in PRL is variable, but may present as decreased lactation
  - gonadotropin insufficiency then causes erectile dysfunction in men, and amenorrhea or infertility in women
  - TSH deficiency produces clinical hypothyroidism
  - ACTH deficiency leads to adrenal insufficiency

Diagnosis by Triple Bolus Test
- stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence IV infusion of insulin, LHRH and TRH
  - insulin → hypoglycemia → increased GH and ACTH
  - LHRH → increased LH and FSH
  - TRH → increased TSH and PRL
THYROID

THYROID STIMULATING HORMONE (TSH)

- glycoprotein
- α subunit similar to those in FSH, LH, hCG, but all have unique β subunits
- stimulates growth of thyroid and secretion of T4 and T3 via cAMP
- regulation
  - stimulated by hypothalamic TRH
  - inhibited by circulating T4, intrapituitary T3, opiates, dopamine

THYROID HORMONES

Biochemistry

- free T4 (0.03%) and free T3 (0.3%) represent the hormonally active fraction
- the remainder is hormonally inactive, mainly bound to thyroxine binding globulin (TBG) and albumin
- T3 is more biologically active than T4
- some T4 is converted to T3 in peripheral tissues by 5'-deiodinase
- metabolized by most tissues; metabolites reach liver and are excreted in bile

Regulation of Thyroid Function

- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
- intrathyroid (autoregulation)
  - response to iodide - with increasing iodide supply, inhibition of iodide organification occurs, thus decreasing T3 and T4 synthesis (Wolff-Chaikoff effect)
  - varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T3 to T4 in iodide deficiency

TESTS OF THYROID FUNCTION AND STRUCTURE

Circulating Thyroid Hormones

- total T3 and T4 levels depend on amount of thyroid binding globulin (TBG)
- TBG increases with: pregnancy, oral contraceptive (OCP) use, acute infectious hepatitis, biliary cirrhosis
- TBG decreases with: androgens, glucocorticoids, cirrhosis, hyponatremia, phenytoin, ASA, NSAIDS, nephrotic syndrome, severe systemic illness
- standard assessment of thyroid function includes TSH and if necessary, free T4 and free T3

TSH

- sensitive TSH (sTSH) is the single best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low and does not rise in response to TRH because of negative feedback from increased levels of circulating T3 and T4
  - secondary: increased TSH
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T3 and T4
  - secondary: TSH is low with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Iodine Kinetics

- an index of thyroid function
- radioactive iodine uptake (RAIU) is high in Graves' disease and low in subacute thyroiditis

Effects of Thyroid Hormones on Peripheral Tissues

- sex hormone binding globulin (non-specific)
  - liver increases production in hyperthyroidism; decreases production in hypothyroidism
- pre-ejection period/ left ventricular ejection time is a measure of the effect of thyroid hormones on the heart
- basal metabolic rate (BMR)

Thyroid Assessment (see Otolaryngology Chapter)

- normal gland size 15-20 g (estimated by palpation)
- thyroid US to detect size of gland, solid vs. cystic nodule
- fine needle aspiration for cytology
- thyroid scan (Technetium99m)
  - for hot vs. cold nodules
  - to distinguish between three major types of high-uptake hyperthyroidism
    - Graves' disease (diffuse uptake)
    - toxic multinodular goiter (multiple discrete areas)
    - solid toxic adenoma (single intense area of uptake)

Miscellaneous Tests

- thyroid antibodies
  - antithyroglobulin antibodies, microsomal antibodies
  - increased in Hashimoto's disease
- TSH receptor antibodies
  - thyroid stimulating immunoglobulin (TSI) or TSAb
  - thyroid stimulating immunoglobulin (TSI) or TSAb
  - increased in Graves' disease
THYROID . . . CONT.

- plasma thyroglobulin level
  - used to monitor thyroid carcinoma activity
  - undetectable levels = remission
  - normal or elevated levels = probable, persistent, recurrent, or metastatic disease
- serum calcitonin
  - not routinely done to investigate most thyroid nodules
  - ordered if suspicious of medullary thyroid carcinoma

HYPERTHYROIDISM

- hyperthyroidism: excess production of thyroid hormone
- thyrotoxicosis: denotes clinical, physiological and biochemical findings in response to elevated thyroid hormone

### Table 11. Differential Diagnosis of Hyperthyroidism

<table>
<thead>
<tr>
<th>Disorder/Disease</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSH</td>
</tr>
<tr>
<td>1. Graves' Disease</td>
<td>decreased</td>
</tr>
<tr>
<td>2. Toxic Nodular Goitre</td>
<td>decreased</td>
</tr>
<tr>
<td>3. Toxic Nodule</td>
<td>decreased</td>
</tr>
<tr>
<td>4. Thyroiditis</td>
<td>decreased</td>
</tr>
<tr>
<td>a) classical subacute thyroiditis</td>
<td></td>
</tr>
<tr>
<td>b) silent thyroiditis</td>
<td></td>
</tr>
<tr>
<td>c) post-partum thyroiditis</td>
<td></td>
</tr>
<tr>
<td>5. McCune-Albright Syndrome</td>
<td>decreased</td>
</tr>
<tr>
<td>6. Jod Basedow (iodine-induced)</td>
<td>decreased</td>
</tr>
<tr>
<td>7. Extra-thyroidal Sources of Thyroid Hormone</td>
<td></td>
</tr>
<tr>
<td>a) endogenous</td>
<td></td>
</tr>
<tr>
<td>i) struma ovariae, ovarian teratoma metastases from follicular carcinoma)</td>
<td></td>
</tr>
<tr>
<td>b) exogenous (drugs)</td>
<td></td>
</tr>
<tr>
<td>8. Excessive Thyroid Stimulation</td>
<td></td>
</tr>
<tr>
<td>a) pituitary thyrotophoma</td>
<td>increased</td>
</tr>
<tr>
<td>b) pituitary thyroid hormone receptor resistance</td>
<td></td>
</tr>
<tr>
<td>c) hCG (e.g. molar pregnancy)</td>
<td>decreased</td>
</tr>
</tbody>
</table>

Clinical Features

- GENERAL: fatigue, heat intolerance, irritability, fine tremor
- CVS: tachycardia, atrial fibrillation, palpitations
  - elderly patients may have only CVS symptoms, commonly new onset atrial fibrillation
- GI: weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
- NEUROLOGY: proximal muscle weakness, hypokalemic periodic paralysis (patients of Oriental origin)
- GU: scant menses, decreased fertility
- DERMATOLOGY: fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (“Plummer’s nails”)
- MUSCULOSKELETAL (rare): decreased bone mass, hypercalcemia
- HEMATOLOGY: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally in Graves’ disease)

A. GRAVES’ DISEASE (see Colour Atlas E2)

- triad of hyperthyroidism with diffuse goiter, ophthalmopathy, dermopathy (need not appear together)
THYROID . . . CONT.

**Epidemiology**
- relatively common, occurs at any age with peak in 3rd and 4th decade
- runs in families
- F > M
- association with HLA B8 and DR3
- may be associated with other autoimmune disorders in family (e.g. pernicious anemia, Hashimoto's disease)

**Etiology and Pathogenesis**
- autoimmune disorder due to a defect in T-suppressor cells
- B-lymphocytes produce thyroid stimulating immunoglobulins (TSI) directed against TSH receptor that mediate thyroid stimulation
- cause of ophthalmopathy uncertain
  - antibodies against extraocular muscle antigens (fibroblasts implicated) with lymphocytic infiltration
  - glycosaminoglycan deposition
- dermopathy may be related to cutaneous glycosaminoglycan deposition
  - pretibial myxedema (see Colour Atlas E3)

**Additional Clinical Features**
- diffuse goiter +/- bruit
- ophthalmopathy: proptosis, lid lag, lid retraction, diplopia, characteristic stare, conjunctival injection
- dermopathy (rare): pretibial myxedema (thickening of dermis)
- acropachy: clubbing and thickening of distal phalanges

**Diagnosis**
- increased free T₄ (and/or increased T₃)
- positive for TSI
- TRH stimulation test (flat TSH response) is diagnostic if sTSH and free T₄ are inconclusive

**Treatment**
- propylthiouracil (PTU) or methimazole (MMI)
  - inhibit thyroid hormone synthesis
  - major side effects: rash, hepatitis and agranulocytosis
- symptomatic treatment with ß-adrenergic antagonists
- thyroid ablation with radioactive ¹³¹I if PTU or MMI trial does not produce disease remission
- subtotal thyroidectomy (indicated rarely for large goiters)
  - risks include hypoparathyroidism and vocal cord palsy
- both MMI and ¹³¹I are contraindicated in pregnancy
- 1/3 of cases achieve long-term remission on drug therapy alone
- small goitre and recent onset are good indicators for long-term remission with medical therapy
- high incidence of hypothyroidism after ¹³¹I, requiring lifelong thyroid hormone replacement
- ophthalmopathy: prevent drying
  - high dose prednisone in severe cases
  - orbital radiation, surgical decompression
  - note that PTU or MMI may worsen ophthalmopathy

**B. SUBACUTE THYROIDITIS (Thyrotoxic Phase)**

**Etiology and Pathogenesis**
- acute inflammation of the thyroid, probably viral in origin, characterized by giant cells and lymphocytes
- often preceded by upper respiratory tract infection (URTI)
- disruption of thyroid follicles by inflammatory process results in the release of stored hormone

**Clinical Features**
- begins with fever, malaise, soreness in neck
- gland becomes enlarged
- two forms
  - painful (“DeQuervain’s”) thyroid, ears, jaw and occiput
  - painless (“Silent”)
- usually transient thyrotoxicosis with a subsequent hypothyroidism phase due to depletion of stored hormone, finally resolving in a euthyroid state over a period of months

**Laboratory**
- elevated T₄, T₃
- radioactive iodine uptake (RAIU) markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses, values consistent with hypothyroidism may appear; rise in RAIU reflects gland recovery

**Treatment**
- ASA can be used for painful form (increases peripheral conversion)
- prednisone may be required for severe pain, fever, or malaise
- ß-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms
- if symptomatically hypothyroid may treat short-term with thyroxine
THYROID . . . CONT.

**Prognosis**
- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis

**C. TOXIC MULTINODULAR GOITRE**
- autonomous thyroid hormone production, may arise from a nodule in a nontoxic multinodular goitre
- may be singular or multiple
- multinodular goitre also known as Plummer's Disease

**Clinical Features**
- goitre with adenomatous changes
- occurs more frequently in elderly people
- atrial fibrillation is a common presentation in the elderly

**Diagnosis**
- thyroid scan with increased uptake in nodule(s), and suppression of the remainder of the gland

**Treatment**
- initiate therapy with antithyroid medications to attain euthyroid state in order to avoid radiation thyroiditis
- then use high dose radioactive iodine to ablate tissue over weeks
- propranolol often necessary for symptomatic treatment prior to definitive therapy (works by blocking the peripheral action of T₃ and T₄)

**D. POSTPARTUM THYROIDITIS**
- a type of painless thyroiditis
- autoimmune-mediated
- occurs in 5-10% of postpartum mothers, one-third of whom develops symptoms
- typical presentation includes thyrotoxicosis 2-3 months postpartum with a hypothyroid phase at 4-8 months; usually resolves spontaneously without need for supplementation
- may be mistakenly diagnosed as postpartum depression
- may recur with subsequent pregnancies
- treat as per painless subacute thyroiditis

**E. THYROTOXIC STORM**
- a severe state of uncontrolled hyperthyroidism, extreme fever, tachycardia, vomiting, diarrhea, vascular collapse and confusion
- often precipitated by infection, trauma, or surgery in hyperthyroid patient

**Differential Diagnosis**
- sepsis
- pheochromocytoma
- malignant hyperthermia

**Clinical Features**
- hyperthyroidism
- hyperthermia, often with dry skin
- arrhythmia → congestive heart failure, pulmonary edema
- mental status changes ranging from delirium to coma

**Laboratory Findings**
- increased T₃, T₄, undetectable TSH
- +/- anemia, leukocytosis, hypercalcemia, elevated LFTs

**Treatment**
- initiate prompt therapy; don't wait for confirmation from lab
- fluid and electrolyte maintenance, vasopressors as indicated
- cooling blanket, acetaminophen for pyrexia
- inderal (decreases peripheral conversion of T₄ to T₃) but watch for CHF
- high dose PTU
- iodide (NaI, KI, Lugol's solution) to inhibit release of thyroid hormone
- dexamethasone to block peripheral conversion and to lower body temperature
- treat precipitant

**Prognosis**
- 50% mortality rate

**HYPOTHYROIDISM**

**Epidemiology**
- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal T₄, TSH mildly elevated)
**THYROID . . . CONT.**

**Differential Diagnosis**
- primary thyroid disease (90%)
  - iatrogenic: post-ablative (131I or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4,000 births)
- pituitary hypothyroidism
  - insufficiency of pituitary TSH
- hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone
  - rare

**Clinical Features**
- GENERAL: fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, enlarged tongue
- CVS: slow pulse, generalized atherosclerosis (increased serum cholesterol and triglycerides), pericardial effusion
- GI: anorexia, weight gain, constipation, poor appetite
- NEUROLOGY: paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes")
- GU: menorrhagia, amenorrhea, anovulatory cycles
- DERMATOLOGY: puffiness of face, periorbital edema, cool, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3)
- HEMATOLOGY: anemia

**Laboratory**
- sensitive TSH (sTSH) is the most sensitive test for primary hypothyroidism
- must measure TSH to rule out secondary or tertiary causes

**Treatment**
- L-thyroxine (dose range usually 0.05 to 0.2 mg/day)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually
- monitor sTSH
- at the optimal replacement dosage, TSH is in the middle of its normal range; can also monitor free T4, particularly in pituitary hypothyroidism

A. **CONGENITAL HYPOTHYROIDISM** (see Pediatrics Chapter)

B. **HASHIMOTO'S THYROIDITIS**
- two variants
  - goitrous: presents with a euthyroid or hypothyroid goitre
  - atrophic: presents initially with hypothyroid state and atrophic gland

**Etiology and Epidemiology**
- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B-lymphocytes produce antithyroglobulin antibody and antithyroid peroxidase (anti-TPO or antimicrosomal antibody)
- associated with HLA B8 and DR3, and other autoimmune diseases (e.g. Sjögren's syndrome, SLE, RA, pernicious anemia, adrenal insufficiency)
- more common in females of middle age and is the most common cause of sporadic goiter in children

**Clinical Features**
- goitrous variant usually presents with a rubbery goitre and euthyroidism,
  then hypothyroidism becomes evident
- atrophic variant patients are hypothyroid from the start
- association with thyroid lymphoma

**Laboratory Findings**
- thyroid function test reveals hypothyroidism, or a euthyroid state with a compensatory increase in TSH, followed by decreased free T4 and eventually decreased free T3
- antimicrosomal and anti-thyroglobulin antibodies

**Treatment**
- if hypothyroid, replace with L-thyroxine
- if euthyroid, also treat with L-thyroxine if significant anti-thyroid antibody present

C. **RIEDEL'S STRUMA**
- rare type of chronic thyroiditis
- fibrotic inflammatory process that extends from the thyroid into surrounding tissues
Clinical Features
- ill-defined, firm mass with possible compressive symptoms of dysphagia, stridor, hoarseness, pain
- chief importance is differentiation from malignancy

Treatment
- surgical wedge resection of the isthmus (to prevent tracheal compression)

D. MYXEDEMA COMA
- most severe complication of hypothyroidism
- generally seen in patients with longstanding unrecognized hypothyroidism and associated with a precipitating event (infection, surgery, MI, CHF)

Clinical Features
- hypothyroidism, stupor, hypoventilation, hypothermia, bradycardia, hypertension

Laboratory Findings
- decreased T3 and T4, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- ABCs
- no active re-warming, but avoid cooling
- NG tube (since ileus often present)
- corticosteroids (due to the possibility of concomitant adrenal insufficiency)
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated
- treat precipitant
- monitor in ICU setting

E. SICK EUTHYROID SYNDROME (SES)
- serious illness, trauma, or stress can induce changes in circulating levels of thyroid hormones
- not due to intrinsic thyroid or pituitary disease
- the abnormalities in SES include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself
- several variants exist
- normal-T4 variant
  - characterized by low T3, normal T4
  - proposed mechanism involves inhibition of peripheral 5’ monodeiodination of T4 to T3
  - differentiated from primary hypothyroidism by a normal TSH
- low-T4 variant
  - characterized by low T3, low T4
  - low T4 likely due to inhibited T4 binding to serum proteins and accelerated metabolic clearance
  - differentiated from primary hypothyroidism with normal or low TSH
  - poorer prognosis
- treat the underlying disease
- thyroid hormone replacement worsens the outcome

NON-TOXIC GOITRE
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes
- appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular nontoxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

Complications
- compression of neck structures, causing stridor, dysphagia, pain, and hoarseness
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism
**Treatment**
- remove goitrogens
- suppression with L-thyroxine may be effective in any TSH-dependent goitre
- surgery may be necessary for severe compressive symptoms

**THYROID NODULES** (see Otolaryngology Chapter)
- clearly defined discrete mass, separated from the thyroid parenchyma

**Etiology**
- benign tumours (e.g. follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

**Investigations**
- fine needle aspiration (FNA)
  - useful only if positive for malignancy (specific, not sensitive)
- thyroid function tests
- thyroid scan
  - 15-20% of cold nodules (minimal $^{131}$I uptake into nodule) are malignant, very low malignant potential if warm or hot (significant $^{131}$I uptake into nodule)

**Figure 3. Workup of Thyroid Nodule**

**THYROID MALIGNANCIES**

**Risk Factors**
- history
  - head or neck irradiation especially during childhood (e.g. acne therapy)
  - family history (especially of medullary carcinoma)
  - rapid growth (and failure to shrink on L-thyroxine)
  - onset < 30 years of age
  - male gender (thyroid nodules more common in females, malignancy more common in males)
  - compressive symptoms (e.g. pain, dysphagia, stridor, hoarseness)
  - cervical lymphadenopathy
  - nodule in patient with Hashimoto’s (must rule out lymphoma)
- physical examination
  - solitary nodule
  - hardness and irregularity of nodule
  - surrounding tissue involvement
  - regional lymphadenopathy
- investigations
  - fine needle aspiration (see Figure 3)
THYROID . . . CONT.

Classification

1. **Papillary Carcinoma (50-70%)**
   - well-differentiated
   - seen more commonly in younger patients
   - may be induced by radiation
   - multicentric, some follicular components histologically
   - usually metastasizes to regional lymph nodes first
   - lifespan not affected if confined to one lobe and < 2 cm
   - remember the "P's": Papillary, Popular, Psammoma, Palpable nodes, Positive Prognosis, Positive $^{131}$I uptake

2. **Follicular Carcinoma (10-15%)**
   - well-differentiated but more aggressive than papillary
   - not associated with radiation exposure
   - tends to be angioinvasive, spreading to lung, bones and distant sites without lymph node involvement
   - most important prognostic factor is invasion, not primary tumour size
   - Hurtle cell cancer: aggressive variant of follicular cancer, frequent pulmonary metastases
   - remember the "F's": Follicular, Far away mets (blood), Female, FNA biopsy not diagnostic, Favourable prognosis

3. **Anaplastic Carcinoma (10%)**
   - occurs most commonly in elderly patients
   - rapidly progressive
   - poor prognosis

4. **Medullary Carcinoma (1-2%)**
   - high familial aggregation, associated with multiple endocrine neoplasia (MEN) Ila or IIb
   - may produce calcitonin, prostaglandins, ACTH, serotonin, kallikrein, bradykinin
     - these substances can be used as tumour markers
   - worse prognosis than papillary or follicular cancer
   - need to screen asymptomatic relatives
     - inappropriate rise in calcitonin with the administration of calcium and pentagastrin
   - remember the "M's": Medullary, MEN Ila or IIb, aMyloid, Median node dissection

5. **Lymphoma (< 1%)**
   - seen in the context of a nodule or an enlarging goitre in a patient with Hashimoto's thyroiditis

Treatment

- lobectomy for small, well-differentiated papillary carcinoma with no evidence of aggressive behaviour or metastases
- near-total thyroidectomy for large tumours with marked angioinvasion or capsular invasion
- nodal dissection required only if nodes present
- generally follow with large dose of ablative radioactive iodine for large, well-differentiated tumours
- thyroid malignancies may be dependent on TSH and may regress with L-thyroxine suppression
- follow thyroglobulin (papillary, follicular), calcitonin (medullary)
- inappropriate serum thyroglobulin level post surgery/ablation may indicate metastases
  - total body $^{131}$I scan will identify metastases
  - treatment by high dose radioactive iodine
ADRENAL CORTEX

ADRENOCORTICOTROPIN HORMONE (ACTH)
- polypeptide
- part of long prohormone (pro-opiomelanocorticropin, POMC) which contains α, β and γ MSH, β-endorphin, and lipotropin as well as ACTH

Physiology
- secretion from pituitary is both pulsatile and diurnally varied, peaking at 0200-0400 hours, lowest at 1800-2400 hours
- stimulates growth of adrenal cortex and secretion of its hormones via cAMP
  - stimulates glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- may have some melanocyte stimulating activity

Regulation
- primary control by CRH from hypothalamus
- feedback inhibition by cortisol on pituitary, hypothalamus and CNS; also regulated by sleep-wake cycle and stress (pyrogens, surgery, hypoglycemia, exercise, severe emotional trauma)

ADRENOCORTICAL HORMONES
- all derived from cholesterol (see Figure 4)
  - mineralocorticoids (aldosterone) from zona glomerulosa (outermost layer = "salt")
  - glucocorticoids (cortisol) from zona fasciculata (middle layer = "sugar")
  - androgens from zona reticularis (innermost layer = "sex")

![Steroid Synthesis Diagram](stereo.png)

**Figure 4. Pathways of Major Steroid Synthesis in the Adrenal Gland and Their Enzymes**

**Aldosterone**
- regulates extracellular fluid (ECF) volume through Na⁺ retention and K⁺ excretion (by stimulation of distal tubule Na⁺/K⁺ ATPase)
- aldosterone regulated principally by the renin-angiotensin-aldosterone system (see Figure 5)
- negative feedback to juxtaglomerular apparatus by long loop (aldosterone via volume expansion) and short loop (angiotensin II via peripheral vasoconstriction)
Glucocorticoids
- secretion regulated by:
  - diurnal variation of ACTH (higher in a.m. than p.m., with peak around 0200 hours)
  - inhibition of both ACTH and CRH release (negative feedback)
  - stress (e.g., fever, pain, hypoglycemia), in addition to stimulating ACTH release, directly stimulates CRH release, over-riding diurnal variation and negative feedback
- 10% free in plasma, 90% bound to transcortin (inactive)
- physiologic effects:
  - stimulate hepatic glucose production (gluconeogenesis)
  - increase insulin resistance in peripheral tissues
  - increase protein catabolism
  - stimulate leukocytosis and lymphopenia
  - inhibit bone formation; stimulate bone resorption
  - inhibit fibroblasts, causing collagen and connective tissue loss
  - suppress inflammation; impair cell-mediated immunity
  - regulate extracellular fluid volume; promote renal solute-free water clearance

Androgens
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione
- peak concentrations in puberty
- proportion of total androgens (adrenal to gonadal) increases in old age
- primarily responsible for adrenarche (pubic and axillary hair)
- adrenal androgen formation is regulated by ACTH (not LH)

TESTS OF ADRENOCORTICAL FUNCTION

Plasma Cortisol
- has diurnal variation; therefore, random measurements are of little value
- response to stimulation or suppression is more informative

24 Hour Urinary Free Cortisol
- correlates well with secretory rates
- good screening test for adrenal hyperfunction

Serum ACTH
- high in primary adrenal insufficiency
- low in secondary adrenal insufficiency

Serum DHEA-S
- the main adrenal androgen

Cosyntropin Stimulation Test
- cosyntropin is an ACTH analogue
- for diagnosing adrenal insufficiency
ADRENAL CORTEX . . . CONT.

Short Cosyntropin Stimulation Test
- 25 U of cosyntropin IM, measure serum cortisol at baseline and at 60 minutes
- POSITIVE response: increase in plasma cortisol level by > 200 nmol/L and an absolute level of > 500 nmol/L (rules out primary adrenal insufficiency)
- NEGATIVE response: may be due to lack of stimulation → proceed to long cosyntropin test

Long Cosyntropin Stimulation Test
- to determine primary vs. secondary adrenal insufficiency
- 25 U of synthetic ACTH infused for 8 hours on 3 consecutive days, cortisol measured qa.m.
- POSITIVE response rules out primary but not necessarily secondary adrenal insufficiency
- NEGATIVE response rules in primary adrenal insufficiency

Metyrapone Test
- one of best tests of integrity of pituitary-adrenal axis, but rarely used
- useful in diagnosing suspected secondary adrenal insufficiency
- 750 mg PO q4h x 24 h; measure serum cortisol, 11-deoxycortisol, and ACTH
- blocks 11-hydroxylase, the final step of cortisol synthesis, causing elevated level of the cortisol precursor, 11-deoxycortisol and decreased serum cortisol levels
- normal response is reduced cortisol, elevated 11-deoxycortisol and elevated ACTH (response of pituitary to decreased cortisol)

Dexamethasone (DXM) Suppression Tests
- gold standard to determine presence and etiology of hypercortisolism
- principle: DXM suppresses pituitary ACTH, so plasma cortisol should be lowered by negative feedback if HPA axis is normal
- if 24 hour urinary free cortisol (screening test) is positive, begin with low-dose DST to confirm diagnosis
- low dose DST: 0.5 mg DXM q8h for 48 hours, then 24 hour urinary free cortisol twice
- following this, measure ACTH; if undetectable, proceed to high-dose DST (8X higher dose than above) to confirm diagnosis of adrenal Cushing's
- if ACTH normal or increased, proceed to a CRF stimulation test via inferior petrosal sinus sampling to distinguish Cushing's disease from ectopic Cushing's syndrome

HYPERALDOSTERONISM
- state of hypersecretion of the mineralocorticoid aldosterone

1. Primary Hyperaldosteronism
- diagnostic criteria:
  - diastolic hypertension without edema
  - decreased renin and increased aldosterone secretion both unresponsive to increases in volume
- aldosterone-producing adrenal adenoma (Conn's syndrome)
- idiopathic bilateral adrenal hyperplasia
- adrenal carcinoma (rare)

Clinical Features
- hypertension uncontrolled by standard therapy
- hypokalemia OFF diuretics
- other symptoms may include
  - polyuria, polydipsia, nocturia
  - fatigue, weakness, paresthesias
  - headaches

Laboratory Findings
- hypokalemia
- high normal Na+
- metabolic alkalosis
- high 24 hour urinary or plasma aldosterone
- low random plasma renin

Treatment
- medical: spironolactone (aldosterone antagonist) or amiloride
- surgical: removal of adenoma is curative

2. Secondary Hyperaldosteronism
- increase in aldosterone in response to activation of renin-angiotensin system
- overproduction of renin (e.g. primary reninism from renin-producing tumour - rare)
- secondary hyperreninism - due to hypoperfusion of kidneys (e.g. renal artery stenosis), or edematous states (CHF, liver cirrhosis), where arterial hypovolemia and/or hypotension is stimulus for aldosterone secretion
  - Bartter's syndrome - severe secondary hyperaldosteronism without edema or hypertension (due to JGA hyperplasia)
ADRENAL CORTEX . . . CONT.

CUSHING’S SYNDROME

- results from chronic glucocorticoid excess (endogenous or exogenous sources)
- endogenous Cushing's syndrome is due to increased cortisol production by the adrenal gland

**Etiology**

- ACTH-dependent: bilateral adrenal hyperplasia and hypersecretion due to
  - ACTH-secreting pituitary adenoma (Cushing's disease)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial carcinoid)
- ACTH-independent
  - long-term use of exogenous glucocorticoids (most common cause of Cushing's syndrome)
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia

**Clinical Features** (see Figure 6, see Colour Atlas E1)

- general
  - truncal (centripetal) obesity, thin extremities, supraclavicular fat pads, posterior cervical fat (“buffalo hump”), “moon facies”
  - hypertension
- skin
  - thin skin, facial plethora, hirsutism in women, wide purple striae, acne, easy bruising, poor wound healing, mucocutaneous candidiasis
- musculoskeletal
  - osteoporosis, pathologic fractures, avascular necrosis (AVN)
  - proximal muscle weakness (more prominent in lower limbs)
- neuropsychiatric
  - emotional lability, depression, euphoria, frank psychosis
- gonadal dysfunction
  - oligomenorrhea / amenorrhea in women, decreased libido / impotence in men
- metabolic
  - glucose intolerance (frank diabetes less common), hyperlipidemia, polyuria, nephrocalcinosis
- ectopic ACTH production
  - hyperpigmentation, hypertension, hypokalemic metabolic alkalosis, weight loss, weakness (typical features of Cushing's syndrome usually absent)

**Figure 6. Cushing’s Syndrome**

Illustration by Marisa Bonofiglio
ADRENAL CORTEX . . . CONT.

Clinical features suspicious for hypercortisolism

- 24 hour urinary free cortisol
  - normal
  - < 4X increase
  - > 4X increase

Cushing's syndrome

- low dose DST to confirm diagnosis
- diagnosis of Cushing's syndrome established

- measure ACTH
  - ACTH increased
  - ACTH decreased

- MRI pituitary, inferior petrosal sinus sampling with CRF stimulation test
- CT adrenal, confirmatory high-dose DST

DST = DXM suppression test

**Figure 7. Hypercortisolism: Algorithm for Diagnosis**

**Treatment**
- pituitary
  - transsphenoidal resection, with glucocorticoid supplement peri- and post-operatively
  - irradiation: only 50% effective, with significant risk of hypopituitarism
- adrenal
  - adenoma: unilateral adrenalectomy (curative)
  - carcinoma: palliative (frequent metastases, very poor prognosis)
- adjunctive chemotherapy often not useful
- ectopic ACTH tumour - usually bronchogenic cancer (a paraneoplastic syndrome)
  - chemotherapy/radiation for primary tumour
  - agents blocking adrenal steroid synthesis: metyrapone or ketoconazole
  - poor prognosis

**CONGENITAL ADRENAL HYPERPLASIA (CAH)** (see Pediatrics Chapter)

**Pathophysiology**
- autosomal recessive pattern of transmission, leading to enzyme defects, which can range from partial to total
- 21-hydroxylase (21-OH) deficiency is the most common form (95%) (see Figure 4)
- results in decreased cortisol and aldosterone with shunting toward adrenal androgen pathway
- deficiency of cortisol leads to elevated ACTH, which increases levels of unaffected steroids and causes bilateral adrenal hyperplasia

**Late-Onset 21-Hydroxylase Deficiency**
- allelic variant of classic 21-hydroxylase deficiency
- mild enzymatic defect
- manifests during or after puberty: signs of androgenization (hirsutism and acne) and amenorrhea or oligomenorrhea
- consider in women with unexplained hirsutism and menstrual abnormalities
- diagnosis
  - increased plasma 17-OH-progesterone after ACTH stimulation test
- treatment
  - dexamethasone, spironolactone (anti-androgen)
  - mineralocorticoid replacement is not needed

**HIRSUTISM AND VIRILIZATION**
- both terms refer to states of androgen excess
- hirsutism
  - male pattern of hair growth in women: back, chest, upper abdomen
- virilization
  - hirsutism, frontal balding
  - clitoral enlargement
  - deepening of voice
  - acne
  - increase in musculature
- defeminization
  - amenorrhea
  - decreased breast size
ADRENAL CORTEX . . . CONT.

**Etiology**
- constitutional
  - most common
  - family history, ethnic background
- medications
  - androgen-mediated: ACTH, anabolic steroids, androgens, progesterational agents
  - non-androgen mediated (hypertrichosis): phenytoin, diazoxide, cyclosporine, minoxidil
- ovarian
  - polycystic ovarian disease (PCOD) (see Gynecology Chapter)
  - tumours
- adrenal
  - congenital hyperplasia (CAH, late-onset CAH)
  - tumours
- Cushing's disease - high ACTH

**Investigations**
- increased testosterone
- DHEA-S as measure of adrenal androgen production
- increased LH/FSH, seen commonly in PCOD as ratio > 2.5

**Treatment**
- cosmetic therapy
- discontinue causative medications
- oral contraceptives
- low dose glucocorticoid
- spironolactone - acts as peripheral androgen antagonist
- cyproterone acetate - blocks androgen receptor binding; being increasingly used in combination with estradiol (Diane-35)

**ADRENOCORTICAL INSUFFICIENCY**

**Primary (Addison's Disease)**
- rare form of adrenal pathology
- most cases are idiopathic
  - likely autoimmune destruction of adrenals (50% of patients have circulating adrenal antibodies)
  - high association with other autoimmune diseases (e.g. chronic lymphocytic thyroiditis, type 1 DM, vitiligo, pernicious anemia)
- metastatic tumour - second commonest cause
- hemorrhagic infarction - coagulopathy in adults or Waterhouse-Friderichsen syndrome in children (meningococcal or Pseudomonas septicemia)
- adrenalectomy
- granulomatous disease (e.g. TB, sarcoidosis)
- infection - particularly AIDS

**Secondary**
- inadequate pituitary ACTH secretion
- multiple etiologies (see Hypopituitarism section), including withdrawal of exogenous steroids that have suppressed pituitary ACTH production

**Clinical Features**
- both primary and secondary
  - weakness and fatigue
  - postural hypotension
  - weight loss, anorexia, nausea/vomiting, diarrhea
  - abdominal, muscle, and joint pain
- primary
  - hyperpigmentation of skin and mucous membranes (e.g. palmar creases and buccal mucosa)
  - dehydration, salt craving
- secondary
  - usually more chronic than primary
  - pallor, normal K+ and hydration
- acute adrenal crisis
  - unable to secrete increased cortisol, ACTH in response to stress (e.g. infection, dehydration, surgery)
  - hypovolemic shock, fever, extreme weakness, decreased LOC, nausea / vomiting, hypoglycemia
ADRENAL CORTEX . . . CONT.

Laboratory Findings
- hyponatremia, hyperkalemia, elevated BUN/creatinine
- chronic anemia (normochromic, normocytic)
- primary
  - low cortisol unresponsive to exogenous ACTH
  - high ACTH
  - adrenal antibodies if autoimmune etiology
- secondary
  - low cortisol, low ACTH
  - usually normal K+, BUN/creatinine

Treatment
- acute condition - can be life-threatening
  - IV NS or D5W/NS in large volumes
  - hydrocortisone 100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factor
- maintenance
  - cortisone acetate 25 mg PO qa.m. and 12.5 mg qp.m.
  - Florinef (synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient
  - increase dose of steroid in times of illness or for surgery

ADRENAL MEDULLA

Catecholamine Metabolism
- catecholamines synthesized from tyrosine in postganglionic sympathetic nerves and chromaffin cells of adrenal medulla
- predominant adrenal catecholamine = epinephrine (adrenaline)
- predominant peripheral catecholamine = norepinephrine (noradrenaline)

PHEOCHROMOCYTOMA

Pathophysiology
- rare tumour arising from chromaffin cells of the sympathetic system
- most commonly a single tumour of adrenal medulla
- 10% extra-adrenal, 10% multiple tumours, 10% malignant, 10% familial
- tumour not innervated but via unknown mechanism, able to synthesize and release catecholamines
- cases sporadic or part of MEN (see Multiple Endocrine Neoplasia section)
- rare cause of hypertension (< 0.1% of all hypertensives)
- curable if recognized and properly treated, but fatal if not

Clinical Features
- symptoms often paroxysmal, may be triggered by stress, exertion, certain foods
- hallmark is paroxysmal or sustained HTN (sustained HTN more common, present between attacks in 60% of patients)
- classic triad: “pounding” headache, palpitations, diaphoresis
- others: tremor, anxiety, chest or abdominal pain, nausea / vomiting

Lab Findings
- increased urinary catecholamines usually sufficient to confirm diagnosis
- elevated plasma epinephrine unsuppressed by clonidine (central α-adrenergic)
- positive adrenal CT scan
- meta-iodo-benzoguanidine (MIBG) uptake by tumour site during scan; useful to locate tumour for surgery

Treatment
- adequate pre-operative preparation
  - α-blockade - PO phenoxycbenzamine (pre-op), IV phentolamine (peri-operative)
  - β-blockade - propranolol
  - volume restoration with vigorous salt-loading
- surgical removal of tumour with careful pre-operative and post-operative ICU monitoring
- rescreen urine one month post-operatively
MULTIPLE ENDOCRINE NEOPLASM (MEN)

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin APUD (amine precursor uptake and decarboxylation) cells
- autosomal dominant inheritance with considerable variability in penetrance and in specific tumour incidences among kindred
- genetic screening methods becoming more available

<table>
<thead>
<tr>
<th>Table 12. MEN Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
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<tr>
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<td>I</td>
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<td>Ila</td>
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<td></td>
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<tr>
<td>IIb</td>
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</tr>
</tbody>
</table>

CALCIUM DISORDERS

CALCIUM HOMEOSTASIS

- serum Ca²⁺ is about 50% protein bound (mostly albumin) and not exchangeable
- alterations in protein content of the blood for any number of reasons
- may affect the total serum Ca²⁺ without altering the ionized form
- normal total serum Ca²⁺ range is 2.25-2.62 mmol/L (9.0-10.5 mg/dL)
- to correct for changes in albumin:
  - corrected Ca²⁺ (mmol/L) = measured Ca²⁺ + 0.25(40-albumin)
- ionic Ca²⁺ levels are maintained within narrow limits (1.15-1.31 mmol/L; 4.6-5.25 mg/dL)
- sources of ECF Ca²⁺: diet, resorption from bone
- loss of Ca²⁺ from ECF space via: GI losses, renal excretion, deposition in bone matrix
- regulated mainly by two factors: parathyroid hormone (PTH) and Vitamin D
- actions mainly on three organs: GI tract, bone, and kidney

Parathyroid Hormone (PTH)

- secretion increased by low serum Ca²⁺ and inhibited by low serum Mg
  - not influenced directly by PO₄ (except by PO₄ effect on the ionic calcium levels)
- major actions
  - increased osteoclast activity → increased Ca²⁺ and increased PO₄
  - increased renal tubular Ca²⁺ (and Mg) reabsorption
  - inhibits renal tubular reabsorption of PO₄ (and HCO₃⁻)
  - increased 1-α-hydroxylase activity → vitamin D → increased Ca²⁺ and PO₄ absorption from gut
  - NET EFFECT: increased serum Ca²⁺ → increased vit D, decreased PO₄

Vitamin D

- necessary for Ca²⁺ and PO₄ absorption from GI tract
- cholecalciferol formed in the skin by the action of UV light
- converted to 25(OH)-vit D by the liver
- converted to 1,25(OH)₂-vit D in the kidney
- production of 1,25(OH)₂-vit D is enhanced by PTH and low PO₄ levels
- if a PTH deficiency exists, metabolism is shunted into the production of 24,25- or 25,26(OH)₂-vit D (relatively inert)
- major actions
  - increased Ca²⁺ and PO₄ absorption from gut
  - increased bone resorption
  - increased osteoclasts
  - increased renal Ca²⁺ reabsorption
  - NET EFFECT: increased serum Ca²⁺ and PO₄
**CALCIUM DISORDERS . . . CONT.**

**Calcitonin**
- polypeptide secreted by thyroid C cells
- secretion enhanced by Ca\(^{2+}\), GI hormones, pentagastrin
- major actions:
  - decreased osteoclastic bone resorption
  - increased renal PO\(_4\) and Na\(^+\) clearance
  - ACUTE NET EFFECT: decreased serum Ca\(^{2+}\) when given in pharmacologic doses

**Magnesium**
- major intracellular divalent cation
- Ca\(^{2+}\) is resorbed from the kidney with Mg, and thus Ca\(^{2+}\) balance is difficult to maintain in Mg deficiency

**Phosphorus**
- found in all tissues and necessary for most biochemical processes as well as bone formation

---

**Table 13. Summary of Effects**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Net Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid Hormone (PTH)</td>
<td>increased Ca(^{2+})</td>
</tr>
<tr>
<td></td>
<td>increased vit D</td>
</tr>
<tr>
<td></td>
<td>decreased PO(_4)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>increased Ca(^{2+})</td>
</tr>
<tr>
<td></td>
<td>increased PO(_4)</td>
</tr>
<tr>
<td>Calcitonin (in pharmacologic doses)</td>
<td>decreased Ca(^{2+})</td>
</tr>
</tbody>
</table>

**HYPERCALCEMIA**

**Definition**
- total corrected serum Ca\(^{2+}\) > 2.62 mmol/L (10.5 mg/dL) OR ionized Ca\(^{2+}\) > 1.35 mmol/L (5.4 mg/dL)
- a medical emergency
  - volume depletion
  - arrhythmias

**Pathophysiology**
- increased bone resorption
- increased gastrointestinal absorption
- decreased renal excretion

**Clinical Features**
- symptoms dependent on the absolute Ca\(^{2+}\) value and the rate of its rise (may be asymptomatic)

---

**Table 14. Symptoms of Hypercalcemia**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
<th>Renal</th>
<th>Neurologic</th>
<th>MSK</th>
<th>Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension</td>
<td>anorexia</td>
<td>polyuria</td>
<td>hypotonia</td>
<td>bone pain (bones)</td>
<td>cognitive changes</td>
</tr>
<tr>
<td>↓ digoxin toxicity</td>
<td>nausea</td>
<td>polydipsia</td>
<td>hyporeflexia</td>
<td></td>
<td>increased alertness</td>
</tr>
<tr>
<td>↓ arrhythmia</td>
<td>(groans)</td>
<td>nephrogenic DI</td>
<td>myopathy</td>
<td></td>
<td>psychosis (moans)</td>
</tr>
<tr>
<td>↓ QT interval</td>
<td>vomiting</td>
<td>nephrolithiasis (stones)</td>
<td>paresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PUD</td>
<td>renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Pearl**
- The symptoms and signs of hypercalcemia include:
  "Bones, Stones, psychosis-based Moans, and abdominal Groans"

**Differential Diagnosis**

---

**Clinical Pearl**
- > 90% of hypercalcemia is caused by either parathyroid disease or malignancy.
1. **Parathyroid Disease**

- **primary hyperparathyroidism**
  - major cause of hypercalcemia
  - PTH hypersecretion causes increase in Ca\(^{2+}\) and bone metabolism/turnover while decreasing PO\(_4\)
  - includes solitary adenoma (most common, 81%), hyperplasia (15%), carcinoma (4%), MEN I and IIa
  - presentation: 50% asymptomatic, renal calculi, neuromuscular disease, decreased bone density and associated consequences
  - investigations: serum Ca\(^{2+}\), PO\(_4\), PTH, diagnostic imaging for renal calculi and osteopenia
  - treatment: continued surveillance vs. surgery
- **secondary hyperparathyroidism**
  - associated with renal failure - due to reduced Vit D synthesis, associated with malabsorption

2. **Malignancy**

- **solid tumours**
  - bone metastases (e.g. breast): mediated by osteoclast activating factor (OAF) and various cytokines
  - humoral mediation of hypercalcemia (e.g. lung and renal cell carcinoma): secondary to production of PTH-related peptides (PTHrp)
- **hematological malignancy** (e.g. multiple myeloma, lymphoma, leukemia)

3. **Vitamin D-Related**

- vitamin D intoxication
- granulomatous diseases (e.g. sarcoidosis)

4. **High Bone Turnover**

- hyperthyroidism
- Paget's disease
- vitamin A excess

5. **Renal Failure**

- milk-alkali syndrome (hypercalcemia with alkalosis and renal failure)
- aluminum intoxication
- **tertiary hyperparathyroidism**
  - persistent increase in PTH after correction of secondary hyperparathyroidism (seen in renal transplant patients)

6. **Drugs**

- thiazides
- lithium
- calcium carbonate
- theophylline

7. **Familial Hypocalciuric Hypercalcemia**

- autosomal dominant
- mutation in Ca\(^{2+}\) sensing receptor gene leads to abnormal sensing of Ca\(^{2+}\) by parathyroid glands and renal tubules (inappropriate secretion of PTH and excessive tubal reabsorption of Ca\(^{2+}\))

**Treatment of Hypercalcemia**

- treatment depends on the Ca\(^{2+}\) level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively
- rehydration and calciuresis
  - IV NS infusion (usually requires 4-5 L of fluid)
  - only after adequately rehydrated, promote calciuresis with a loop diuretic, i.e. furosemide
- bisphosphonates
  - treatment of choice
  - inhibit osteoclast activity
  - indicated in malignancy-related hypercalcemia
  - pamidronate is most commonly used
  - IV route since poorly absorbed from the GI tract
  - several days until full effect but effect is long-lasting
- mithramycin
  - effective when patient cannot tolerate large fluid load (dangerous - hematotoxic and hepatotoxic)
- calcitonin
  - inhibits osteoclastic bone resorption and promotes renal excretion of calcium
  - acts rapidly but often transient response
  - combination of calcitonin and steroids may prolong reduction in calcium
  - tachyphylaxis may occur
- steroids
  - anti-tumour effects
  - useful in vitamin D-related hypercalcemia (including sarcoidosis) and hematogenous malignancies (myeloma, lymphoma)
  - slow to act (5-10 days); need high dose
- prostaglandin inhibitors
- surgical treatment if indicated
- avoid immobilization
HYPOCALCEMIA

Definition
- total corrected serum Ca\(^{2+}\) < 2.25 mmol/L (9.0 mg/dL)

Clinical Features
- most characteristic symptom is tetany
- differential diagnosis of tetany
  - metabolic alkalosis (with hyperventilation)
  - hypokalemia
  - hypomagnesemia

Table 15. Signs and Symptoms of Hypocalcemia

<table>
<thead>
<tr>
<th>Acute Hypocalcemia</th>
<th>Chronic Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>paresthesias</td>
<td>CNS: lethargy, seizures, psychosis, basal ganglia calcification</td>
</tr>
<tr>
<td>hyperreflexia</td>
<td>extrapyramidal effects, papillae, pseudotumour cerebri</td>
</tr>
<tr>
<td>tetany</td>
<td>CVS: prolonged QT interval</td>
</tr>
<tr>
<td>laryngospasm (with stridor)</td>
<td>GI: malabsorption, diarrhea</td>
</tr>
<tr>
<td>confusion</td>
<td>Skin: dry, scaling, alopecia, brittle and fissured nails, moniliasis, abnormal dentition</td>
</tr>
<tr>
<td>Chvostek's sign (tap CN VII)</td>
<td>Ocular: cataracts, papillae</td>
</tr>
<tr>
<td>Trousseau's sign (carpal spasm)</td>
<td></td>
</tr>
</tbody>
</table>

Differential Diagnosis

1. Deficient PTH Action
- results in
  - decreased bone resorption
  - decreased intestinal Ca\(^{2+}\) absorption
  - increased renal Ca\(^{2+}\) excretion
- iatrogenic hypoparathyroidism
  - post-thyroidectomy/\(^{131}\)I ablation
- idiopathic/autoimmune hypoparathyroidism
  - congenital (DiGeorge syndrome) - dysgenesis of thymus and parathyroid glands
  - acquired (polyendocrine autoimmune disease - hypoparathyroidism
  - ± adrenal insufficiency ± gonadal failure ± hypothyroidism and rarely hypopituitarism, diabetes insipidus, type 1 DM)
- hemochromatosis
- pseudohypoparathyroidism
  - PTH resistance secondary to Gs protein deficiency
- severe hypomagnesemia
  - normally low Mg level stimulates PTH secretion, but chronic hypomagnesemia is paradoxically associated with impaired PTH secretion
  - low Mg levels also impair peripheral responsiveness to PTH

2. Deficient Vitamin D Action
- decreased intestinal absorption
- vitamin D deficiency
- receptor defect (vitamin D-dependent rickets type II)
- hydroxylation defects
  - congenital: type I rickets
  - acquired: chronic renal failure (CRF), hepatic failure

3. Renal Disease
- most common cause of hypocalcemia; increased loss of Ca\(^{2+}\)
- chronic renal failure, nephrotic syndrome, acute renal failure

4. Drugs
- phosphate
- calcitonin
- aminoglycosides
- antineoplastic drugs (cisplatin, mithramycin)
- loop diuretics

5. Alcoholism

6. Acute Pancreatitis
- saponification of Ca\(^{2+}\) by lipids
CALCIUM DISORDERS . . . CONT.

7. Pregnancy
- low total Ca\(^{2+}\) (due to hypoalbuminemia) but normal ionized level

Treatment of Hypocalcemia
- correct underlying disorder
- acute/severe hypocalcemia
  - calcium gluconate (generally requires continuous infusion)
  - goal is to raise Ca\(^{2+}\) to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH
- if PTH recovery not expected, requires long-term therapy with vitamin D and calcium
- do not correct hypocalcemia if it is suspected to be a transient response

METABOLIC BONE DISEASE

OSTEOPOROSIS

Definition
- an age-related condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to bone fracture

Pathophysiology
- bone resorption > bone formation/remodelling

Risk Factors
- low peak bone mass
  - small Caucasian or Asian female
  - family history
- estrogen-related bone mass
  - early menopause
  - oophorectomy
  - amenorrhea
- advanced age
- secondary to medical disease
- other
  - diet, smoking, alcohol, caffeine
  - minimal weight-bearing physical activity

Classification

1. Primary Osteoporosis
- usually in women, within 20 years after menopause
- affects mainly trabecular bone

2. Secondary Osteoporosis
- endocrinopathies
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - diabetes
  - acromegaly
- malignancy
  - multiple myeloma
- gastrointestinal disease
  - malabsorption
  - liver disease
- drugs
  - steroids
  - phenytoin
  - chronic heparin
- other
  - rheumatoid arthritis
  - renal disease
  - poor nutrition
  - immobilization

Clinical Features
- commonly asymptomatic
- pain, especially backache
- collapsed vertebrae —> height loss
- fractures
  - hip, vertebrae, humerus, and wrists most common
- Dowager's hump = collapse fracture of vertebral bodies in mid-dorsal region
METABOLIC BONE DISEASE . . . CONT.

Investigations
- laboratory
  - usually normal serum Ca\(^{2+}\), PO\(_4\), alkaline phosphatase
- densitometry
  - single-energy x-ray absorptiometry, dual-energy x-ray absorptiometry (most useful), quantitative CT, ultrasonography
  - lumbar spine and views of femur
  - compared to controls
- 1-2.5 SD = osteopenia
- > 2.5 SD = osteoporosis

Treatment
- not very satisfactory
- prevention and lifestyle modification
  - safety measures to prevent falls
  - weight-bearing exercises
  - vitamin D with Ca\(^{2+}\) supplementation
  - limits to smoking and alcohol use
- measures to decrease further bone loss/bone resorption
  - postmenopausal estrogen replacement
  - Ca\(^{2+}\) supplementation (1,000-1,500 mg/day for postmenopausal women)
  - bisphosphonates - inhibitors of osteoclast binding
  - calcitonin - osteoclast receptor binding
  - thiazide diuretics (for hypercalcuria)
  - combination therapy (synergistic): estrogen + bisphosphonate
- measures to increase bone mass
  - fluoride - stimulates osteoblasts for bone formation
  - parathyroid hormone

OSTEOMALACIA AND RICKETS

Definitions
- abnormal concentration of ions leads to higher proportion of osteoid (unmineralized) tissue
- disease prior to epiphyseal closure (in childhood) = rickets
- disease after epiphyseal closure (in adulthood) = osteomalacia

Etiology
- vitamin disorders
  - decreased availability of vitamin D
    - insufficient sunlight exposure
    - nutritional deficiency
    - malabsorption
    - hydroxylation defects
    - nephrotic syndrome
  - liver disease
  - chronic renal failure
  - anticonvulsant therapy
- mineral deficiencies
  - Ca\(^{2+}\) deficiency
  - PO\(_4\) deficiency
    - decreased GI absorption
    - increased renal loss
- disorders of bone matrix
- inhibitors of mineralization
  - aluminum
  - bisphosphonates

Table 16. Clinical Presentations of Rickets and Osteomalacia

<table>
<thead>
<tr>
<th>Rickets</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>skeletal deformities, bowlegs</td>
<td>not as dramatic</td>
</tr>
<tr>
<td>fracture susceptibility</td>
<td>diffuse skeletal pain</td>
</tr>
<tr>
<td>weakness and hypotonia</td>
<td>bone tenderness</td>
</tr>
<tr>
<td>disturbed growth</td>
<td>fractures</td>
</tr>
<tr>
<td>rachitic rosary</td>
<td>gait disturbances</td>
</tr>
<tr>
<td>(prominent costochondral junctions)</td>
<td>proximal muscle weakness</td>
</tr>
<tr>
<td>Harrison's groove</td>
<td>indentation of lower ribs</td>
</tr>
<tr>
<td>(indentation of lower ribs)</td>
<td>hypocalcemia</td>
</tr>
<tr>
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</tbody>
</table>
METABOLIC BONE DISEASE . . . CONT.

Investigations
- laboratory
  - decreased serum Ca$^{2+}$
  - decreased serum phosphorus
  - increased serum alkaline phosphatase (ALKP)
  - decreased urinary Ca$^{2+}$
- radiologic findings
  - pseudofractures – thought to be healed microfractures
  - radiolucent banding of spine
- bone biopsy
  - usually not necessary but considered the gold standard for diagnosis

Treatment
- depends on the underlying cause
- vitamin D supplementation
- PO$_4$ supplements if low serum PO$_4$ is present
- Ca$^{2+}$ supplements for isolated calcium deficiency
- HCO$_3$ if chronic acidosis

RENAL OSTEOODYSTROPHY

Pathophysiology
- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)$_2$-vit D synthesis) and loss of renal mass (reduced 1-$\alpha$-hydroxylase)

Types
- produces a mixture of four types of bone disease
  - osteomalacia - from acidosis and retention of toxic metabolites
  - osteoporosis - metabolic acidosis dissolution of bone buffers
  - osteitis fibrosa cystica - from increased PTH
  - osteosclerosis - from increased PTH
- metastatic calcification secondary to hyperphosphatemia may occur

Clinical Features
- soft tissue calcifications —>- necrotic skin lesions if vessels involved
- osteodystrophy —> bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Treatment
- prevention
  - maintenance of normal serum Ca$^{2+}$ and PO$_4$ by restricting PO$_4$ intake to 1 g/day
  - Ca$^{2+}$ supplements
  - PO$_4$ binding agents
  - prophylactic use of vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

PAGET’S DISEASE OF BONE

Definition
- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
- a common disease: 5% of the population, 10% of population > 80 years old

Etiology
- postulated to be related to a slow viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence

Pathophysiology
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Clinical Features
- usually asymptomatic (routine x-ray finding or elevated alkaline phosphatase)
- severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
- skeletal deformities – bowed tibias, kyphosis, frequent fractures
- skull involvement – headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity
Investigations
- laboratory
  - serum alkaline phosphatase is usually very high
  - normal or increased serum Ca²⁺
  - normal serum PO₄
  - increased urinary hydroxyproline (indicates resorption)
- imaging
  - evaluate the extent of disease with bone scan
  - initial lesion may be destructive and radiolucent
  - involved bones are expanded and denser than normal
  - multiple fissure fractures in long bones

Differential Diagnosis
- primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

Complications
- fractures
- hypercalcemia and nephrolithiasis
- cranial nerve compression and palsies, e.g. deafness
- spinal cord compression
- osteosarcoma/sarcomatous change
  - 1-3%
  - indicated by marked bone pain, new lytic lesions and sudden increased alkaline phosphatase
- high output congestive heart failure due to increased vascularity
- osteoarthritis

Treatment
- symptomatic therapy
- calcitonin
- bisphosphonates, e.g. alendronate

MALE REPRODUCTIVE ENDOCRINOLOGY

Androgen Regulation
- both positive and negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from the Leydig cell) primarily involved in negative feedback on LH, whereas inhibin (from the Sertoli cell) suppresses FSH secretion

TESTS OF TESTICULAR FUNCTION
- testicular size (lower limit = 4 x 2.5 cm)
- serum LH, FSH, testosterone
- hCG stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
  - semen volume
  - sperm count, morphology and motility
- testicular biopsy
  - indicated in the context of normal FSH and azoospermia/oligospermia

HYPOGONADISM
- deficiencies in gametogenesis or the secretion of gonadal hormones

Etiology
1. Hypergonadotropic Hypogonadism
   (Primary Testicular Failure)
   - characterized by increased LH/FSH
   - congenital
     - chromosomal defects, i.e. Klinefelter syndrome, Noonan syndrome
     - cryptorchidism
     - male pseudohermaphroditism
     - bilateral anorchia
MALE REPRODUCTIVE ENDOCRINOLOGY . . . CONT.

- germ cell defects
  - Sertoli cell only syndrome (arrest of sperm development)
  - Leydig cell aplasia/failure
- inflammation
  - orchitis – mumps, tuberculosis, lymphoma, leprosy
  - genital tract infection
- physical factors
  - trauma, heat, irradiation
- drugs
  - marijuana, alcohol, chemotherapeutic agents
- myotonic dystrophy
- defects in androgen biosynthesis
- idiopathic

2. Hypogonadotropic Hypogonadism (Hypothalamic Pituitary Failure)
- characterized by decreased or normal LH
- congenital
  - Kallman's syndrome, Prader-Willi syndrome
- constitutional delay
- endocrine
  - Cushing's syndrome
  - hypothyroidism
  - hypopituitarism (pituitary tumours, hypothalamic lesions, hemochromatosis)
  - estrogen-secreting tumours (testicular, adrenal)
- drugs
  - alcohol
  - marijuana
  - spironolactone
  - ketoconazole
  - GnRH agonists
- prior androgen use
- chronic illness
- malnutrition
- idiopathic

3. Defects in Androgen Action
- complete androgen insensitivity (testicular feminization)
- incomplete androgen insensitivity
  - 5α-reductase deficiency

Clinical Presentation
- depends on age of onset
- fetal life
  - ambiguous genitalia and male pseudohermaphroditism
- prepubertal
  - poor secondary sexual development, poor muscle development
  - eunuchoid skeletal proportions (upper/lower segment ratio < 1; arm span/height ratio > 1)
- postpubertal
  - decreased libido, erectile dysfunction, infertility
  - decreased facial and body hair if very significant androgen deficiency (very low levels required to maintain sexual hair)
  - fine wrinkles in the corners of mouth and eyes
  - osteoporosis with longstanding hypogonadism

Treatment
- consider testosterone replacement

INFERTILITY (see Urology Chapter)

ERECTILE DYSFUNCTION (see Urology Chapter)

GYNECOMASTIA
- proliferation of the glandular component of the male breast
- estrogen/androgen imbalance - increased estrogen/androgen ratio

Etiology
- physiologic
  - neonatal (maternal hormone)
  - puberty
  - aging
pathologic
  • endocrinopathies - primary hypogonadism, hyperthyroidism
    extreme hyperprolactinemia, adrenal disease
  • tumours - pituitary, adrenal, testicular, breast
  • chronic diseases - liver, renal, malnutrition, etc.
  • drugs - spironolactone, cimetidine, digoxin, chemotherapy, marijuana
  • congenital/genetic - Klinefelter's syndrome
  • other - idiopathic, familial

Investigations
- history
  • age, onset, duration, pain, family history, chronic diseases, drugs
- physical examination
  • general health, feminization
  • breast, thyroid, adrenal, liver, testicular exams
- investigations
  • laboratory - serum TSH, PRL, LH, FSH, free testosterone, estradiol, LFTs
  • CXR to rule out tumour
  • testicular U/S to rule out testicular mass

Treatment
- medical
  • correct the underlying disorder, discontinue responsible drug
  • androgens for hypogonadism
  • anti-estrogens - tamoxifen, clomiphene
- surgical
  • usually required if gynecomastia present for > 1 year
  • reduction mammoplasty

REFERENCES


<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Mechanism of action</th>
<th>Indications</th>
<th>Major Side Effects</th>
<th>Contraindications</th>
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</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
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<td>(see Table 2)</td>
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<td>Biguanides</td>
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<td>(see Table 2)</td>
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<td>Thyroid Hormones</td>
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<td>L-thyroxine</td>
<td>Synthroid</td>
<td>replace deficient thyroid hormone</td>
<td>hypothyroidism, thyroid suppression</td>
<td>induced hyperthyroidism</td>
<td>caution in heart disease</td>
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<tr>
<td>Thionamides</td>
<td>1. propylthiouracil (PTU)</td>
<td>Propyl-Thyracil, inhibits organification of iodine and therefore synthesis of thyroid hormones</td>
<td>hyperthyroidism</td>
<td>acute - headache, nausea, chronic - rash, hepatitis, agranulocytosis</td>
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<td>2. methimazole (MMI)</td>
<td>Tapazole, inhibits organification of iodine and therefore synthesis of thyroid hormones</td>
<td>hyperthyroidism</td>
<td>agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia</td>
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<tr>
<td>HMG Co-A Reductase Inhibitors</td>
<td>lovastatin simvastatin pravastatin atorvastatin</td>
<td>Mevacor, Zocor, Pravachol, Lipitor</td>
<td>decrease cholesterol synthesis</td>
<td>elevated total and LDL cholesterol, 2nd prevention of MI</td>
<td>GI symptoms, rash, pruritus, elevated LFTs, myositis (uncommon)</td>
<td>active liver disease, persistent elevated transaminases</td>
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<tr>
<td>Fibric Acid Derivatives</td>
<td>gemfibrozil fenofibrate</td>
<td>Lopid, Lipidil</td>
<td>decrease VLDL, increase HDL levels</td>
<td>hypertriglyceridemia, hypercholesterolemia</td>
<td>GI upset, enhances gallstone formation</td>
<td>hepatic and renal dysfunction</td>
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<tr>
<td>Niacin Derivatives</td>
<td>nicotinic acid</td>
<td>decreases synthesis of VLDL and dearance of HDL</td>
<td>used for a variety of hyperlipidemias</td>
<td>generalized flushing, abnormal LFTs, pruritus, worsening glucose tolerance severe hypertension</td>
<td>hypersensitivity, hepatic dysfunction, active peptic ulcer disease, overt DM, hyperuricemia</td>
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<tr>
<td>Other Lipid Lowering Drugs</td>
<td>probucol</td>
<td>Loreco</td>
<td>decreases LDL, anti-oxidant</td>
<td>increased LDL, mixed hyperlipidemia</td>
<td>decreased HDL, diarrhea, flatulence, abdominal pain, nausea and vomiting</td>
<td>pregnancy</td>
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<tr>
<td>Resin Binders</td>
<td>cholestyramine</td>
<td>Questran</td>
<td>absorbs and binds bile acids which are excreted, decreasing enterohepatic circulation</td>
<td>elevated LDL</td>
<td>GI symptoms - constipation, nausea, flatulence, bloating</td>
<td>complete biliary obstruction, pregnancy, lactation</td>
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<tr>
<td>Prolactin Inhibitors</td>
<td>bromocriptine cabergoline</td>
<td>Parlodel, Dostinex</td>
<td>dopamine analogue</td>
<td>prolactinoma, galactorrhea, inhibition of lactation, acromegaly</td>
<td>nausea and vomiting, headaches</td>
<td>uncontrolled hypertension, pre-eclampsia</td>
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<td>ADH Analogues</td>
<td>desmopressin</td>
<td>DDAVP</td>
<td>stimulates tubular water reabsorption transient increase in clotting factor VIII</td>
<td>central DI, enuresis, hemostasis for hemophilia A and vWD type I</td>
<td>headache, tachycardia, hypotension, decreased urine output, hyponatremia</td>
<td>hypersensitivity</td>
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<tr>
<td>Vitamin D</td>
<td>calcitriol</td>
<td>Rocaltrol</td>
<td>increased osteoclast action, renal Ca(^{2+}) absorption, bone resorption, Ca(^{2+}) and PO(^{4-}) absorption from gut, increased serum Ca(^{2+}) and PO(^{4-})</td>
<td>hypocalcemia, osteodystrophy, osteoporosis</td>
<td>metallic taste, epigastric discomfort, nausea and vomiting</td>
<td>hypercalcemia</td>
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<tr>
<td>Bisphosphonates</td>
<td>1. pamidronate disodium</td>
<td>Aredia (APD)</td>
<td>osteoclast inhibitor</td>
<td>tumour induced hypercalcemia</td>
<td>infusion site reaction transient decrease in Ca(^{2+})</td>
<td>hypersensitivity</td>
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<tr>
<td></td>
<td>2. alendronate</td>
<td>Fosamax</td>
<td>osteoclast inhibitor</td>
<td>osteoporosis</td>
<td>GI upset, esophagitis</td>
<td>severe renal dysfunction</td>
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<td>3. etidronate</td>
<td>Didrocal</td>
<td>osteoclast inhibitor</td>
<td>Paget's disease; used in cyclic fashion for osteoporosis as it may inhibit bone formation</td>
<td>severe renal dysfunction</td>
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<td>4. risedronate</td>
<td>Actonel</td>
<td>osteoclast inhibitor</td>
<td>osteoporosis</td>
<td>arthralgia, diarrhea, headache</td>
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<td>Steroids</td>
<td>A. Glucocorticoids</td>
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<tr>
<td></td>
<td>1. prednisone (5 mg)</td>
<td>many</td>
<td>anti-inflammatory effect via unclear mechanisms</td>
<td>adrenal insufficiency, autoimmune disorders, COPD/ asthma, ITP, nephrotic syndrome, dermatological disorders, cerebral edema, prevention of organ transplant rejection, gout, chemotherapy, ocular inflammation</td>
<td>electrolyte disturbances, fluid retention, immunosuppression, muscle weakness, impaired wound healing, PUD, menstrual irregularities, psychosis, osteoporosis, AVN, many drug interactions</td>
<td>systemic fungal infection</td>
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<td>2. methylprednisolone (4 mg)</td>
<td>Solumedrol</td>
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<td>3. hydrocortisone (25 mg)</td>
<td>Solucortef</td>
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<td>4. dexamethasone (0.75 mg)</td>
<td>Decadron</td>
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<tr>
<td></td>
<td>fluocortisone</td>
<td>Florinef</td>
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<td>B. Mineralocorticoids</td>
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