69. Hypothalamic/Pituitary Hormones – Rana
70 & 71. Estrogens & Progesterone I & II – Rana
72. Androgens – Rana
73 & 74. Diabetes Drugs I & II – Clipstone
75. Adrenocorticosteroids & Antagonists – Clipstone
76. Thyroid/Anti-thyroid Drugs – Patel
77. Calcium Metabolism - Patel
Date: Thursday, March 19, 2015-8:30 AM
Reading Assignment: Katzung, Chapter 37

Key Concepts and Learning Objectives

- To review the physiology of neuroendocrine regulation
- To discuss the use neuroendocrine agents for the treatment of representative neuroendocrine disorders:
  - growth hormone deficiency/excess, infertility, hyperprolactinemia

Drugs discussed

Growth Hormone Deficiency:
- Recombinant hGH
- Synthetic GHRH, Recombinant IGF-1

Growth Hormone Excess:
- Somatostatin analogue
- GH receptor antagonist
- Dopamine receptor agonist

Infertility and other endocrine related disorders:
- Human menopausal and recombinant gonadotropins
- GnRH agonists as activators
- GnRH agonists as inhibitors
- GnRH receptor antagonists

Hyperprolactinemia:
- Dopamine receptor agonists
1. Overview of Neuroendocrine Systems

The neuroendocrine system controlled by the pituitary and hypothalamus controls major body functions.

- The communication from the hypothalamus to anterior pituitary (AP) is via vascular link: hypothalamic-pituitary-portal-system.
- The hormones of the posterior lobe of pituitary are synthesized in the hypothalamus, transported to the posterior pituitary, and released into circulation in response to specific physiologic signals.

2. Regulation of Anterior Pituitary (AP) Secretion:

Key Concepts:

A. Clusters of neurosecretory cells in the hypothalamus synthesize specific “releasing” or “inhibiting” factors or hormones, which are released into the hypothalamic-pituitary-portal-system by action potentials.
B. These hypothalamic (hypophysiotropic) hormones signal release or inhibition of release of AP hormones (except Prolactin)
C. Hormones released from AP stimulate hormone production by a peripheral endocrine gland or the liver (except Prolactin)
D. Each pathway, including a hypothalamic factor(s), pituitary gland factor(s), and the ultimate target gland is referred to as an endocrine axis.
E. There are 5 endocrine axes.
E. All these hormones function through G protein coupled receptors, and GH and prolactin act through JAK/STAT receptors.

F. End-product feedback inhibition tightly controls hormone release from hypothalamus and pituitary gland via Long, Short and Ultra-short loops.

3. Hypothalamic-Pituitary-Growth Hormone Axis
A. Physiological Actions of Growth Hormone (GH)

- **In childhood:** GH promotes linear growth, growth of long bones, cartilage, muscle, organ systems; it is a major determinant of adolescent growth spurt.

- **In adulthood major effects are metabolic:** It increases protein synthesis and bone density; promotes lipolysis and inhibits lipogenesis; promotes gluconeogenesis and glucose release; opposes insulin-induced glucose uptake in adipose tissue, reduces insulin sensitivity.

- GH is released in a pulsatile manner, mostly during sleep. Pulses are generated by interplay of GHRH and Somatostatin.

- GH secretion decreases with age.

- **Mechanism of Action:**
  - Binding of GH to its receptor activates the signaling cascade mediated by receptor associated JAK tyrosine kinases and STATs.
  - The effects of GH are primarily mediated by insulin-like growth factor 1 (IGF-1), released from liver in response to GH.

B. Disorders of Hypothalamic-Pituitary-Growth Hormone Axis

**Features of Growth Hormone Deficiency**

1. **In Children,** results in short stature and adiposity, hypoglycemia. This is most commonly due to a deficiency of GHRH.

2. **In Adults:** This results in
   - Changes in body composition: increased generalized adiposity
   - Decreased skeletal muscle mass and strength
   - Decreased bone density
   - Cardiovascular changes; cardiac muscle atrophy, atherogenic blood lipid profile
   - Fatigue, weakness, depression, overall malaise

   This might be due to a continuation of childhood-onset disease; adult-onset is usually pituitary problem.

**Pharmacology of Growth Hormone Deficiency**

**Drugs Used:**

- Synthetic GHRH (Sermorelin)
- **Recombinant human growth hormone** (Somatropin, Somatrem)
- Recombinant IGF1 (Mecasermin)
**Treatment with synthetic GHRH (Sermorelin)**

Sermorelin is used if a patient possesses defective hypothalamic release of GHRH but normally functioning anterior pituitary somatotrophs.

**Treatment with Recombinant Human Growth Hormone (Somatropin, Somatrem)**

**Drug Description:**
- Most cases of GH deficiency are treated with replacement of recombinant human growth hormone (rhGH). They are:
  1. **Somatropin** (synthetic growth hormone), which is a 191-amino acid peptide, identical to the native form of hGH
  2. **Somatrem**, which is a 192-amino acid peptide consisting of 191aa of GH plus an extra methionine residue at the N-terminus

**Mechanism of Action:**
- It replaces GH

**Drug Indications:**
- Documented growth failure in pediatric patients associated with: GH deficiency, chronic renal failure, Prader-Willi syndrome, Turner syndrome
- Small-for-gestational-age condition
- Idiopathic short stature, non GH-deficient (>2.25 S.D. below mean height for age/sex)
- GH deficiency in adults
- Wasting in patients with AIDS
- Short bowel syndrome in patients who are also receiving specialized nutritional support

**Efficacy:**
- **Children**
  - Increases linear growth, weight gain to low normal range
  - Increases muscle mass, organ size, RBCs

- **Adults**
  - Increases bone mineral density
  - Normalizes body composition: decreased central adiposity
  - Increases muscle mass and strength
  - Improves lipid profile and cardiac function
  - Improves psychological symptoms and sense of well being

**Side Effects:**
- Leukemia, rapid growth of melanocytic lesions
- Hypothyroidism
- Insulin resistance
- Arthralgia
- Increase in cytochrome P450 activity

**Contraindications:**
- Pediatric patients with closed epiphyses
- Active underlying intracranial lesion
- Active malignancy
- Proliferative diabetic retinopathy
Treatment with Recombinant IGF1 (Mecasermin)

Mecasermin is used for children with severe IGF1 deficiency due to mutations in the GH receptor (Laron dwarfism) or development of neutralizing antibodies against GH.

Features of Growth Hormone Excess

This usually results from benign tumor of the anterior pituitary.

1. **In children:** It causes **gigantism.**
   - This occurs before the closure of epiphyses, because excess IGF1 causes excessive longitudinal bone growth

2. **In adults:** It causes **acromegaly.**
   - This occurs after epiphyses close, because excess IGF1 although can no longer stimulate long bone growth, can still promote growth of deep organs and cartilaginous tissue. This is characterized by:
     - Thickening of bones, esp. face, hands
     - Large facial structure, macroGLOSSia and hepatomegaly
     - Increased soft tissue growth
     - Enlarged, arthritic joints
     - Headache, sleep apnea, excessive sweating
     - Increased risk of CV disease, GI cancers (esp. colon), reproductive disorders

Pharmacology of Growth Hormone Excess

Standard treatment for larger pituitary adenoma is transsphenoidal surgery to remove the tumor. Medical options for smaller adenomas are as follows:

**Drugs Used:**
- Somatostatin analogues (Octreotide, Lanreotide in Europe)
- GH receptor antagonist (Pegvisomant)
- Dopamine receptor agonist (Bromocriptine - described under hyperprolactinemia)

Treatment with Somatostatin Analogue (Octreotide)

**Drug Description:**
- Somatostatin analogues:
  - Somatostatin physiologically inhibits GH secretion, but is rarely used clinically, since it has a very short half-life (a few minutes)
  - Octreotide is a synthetic long-lasting peptide analogue of somatostatin (45 times more potent)

**Mechanism of Action:**
- It inhibits GH secretion

**Drug Indications:**
- Used to control pituitary adenoma growth in acromegalic patients
- Carcinoid crisis- flushing, diarrhea and all symptoms of carcinoid syndrome
- Secretory Diarrhea from vasoactive intestinal peptide-secreting tumors
- To control acute GI bleeding
Side Effects:
- Nausea, vomiting, abdominal cramps, GI discomfort
- Cardiac effects include sinus bradycardia and conduction disturbances
- Hypoglycemia
- Gallstone formation

Contraindications:
- Hypersensitivity to octreotide

D. Treatment with GH Receptor Antagonist (Pegvisomant)

Drug Description:
- Pegvisomant is a GH receptor antagonist, recombinant protein, 191 amino acids
- Has multiple polyethylene glycol (PEG) residues, which prolongs its half-life

Mechanism of Action:
- Pegvisomant is a competitive antagonist of GH activity
- This can bind to the transmembrane GH receptor but cannot activate subsequent intracellular signaling
- It decreases serum IGF1 levels

Drug Indications:
- Used for the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention.

Side Effects:
- Increased pituitary adenoma size
- Elevated serum aminotransferase levels

Contraindications:
- Hypersensitivity to pegvisomant

4. Hypothalamic-Pituitary-Reproductive Axis

A. Physiological Actions of Gonadotropins

The gonadotroph cells in the pituitary secrete two types of gonadotropins in response to pulsatile GnRH:
- LH (Luteinizing hormone)
- FSH (Follicle-stimulating hormone)

In Women:
The main function of FSH is ovarian follicle development. In the follicular stage of the menstrual cycle, LH stimulates androgen production in the ovary (Thecal cells), whereas FSH stimulates conversion of androgens to estrogens (Granulosa cells). In the luteal phase, estrogen and progesterone production is primarily controlled by LH, and during pregnancy controlled by hCG (human chorionic gonadotropin) produced by the placenta.
In Men:
FSH primarily regulates spermatogenesis. LH stimulates production of testosterone by the testicular Leydig cells. In Sertoli cells, FSH produces androgen binding protein, which helps to maintain high testicular levels of testosterone.

B. Disorders of Hypothalamic-Pituitary-Reproductive Axis

Key Concepts:
- In both men and women, infertility due to neuroendocrine factors may respond to pharmacological treatment if the gonads are competent to respond in a normal physiologic manner.
- Pharmacological treatments are also used in assisted reproductive technologies in women with genital tract/tubal abnormalities.

Pharmacology of Female and male Infertility

Drugs Used:

Stimulation
- Gonadotropins (human menopausal gonadotropins or menotropins, human chorionic gonadotropin or hCG, Urofollitropin, Follitropin)
- Gonadotropin Releasing Hormone (GnRH) or its analogue Gonadorelin with short-half life (4 minutes)- pulsatile form

Inhibition
- Synthetic analogs of GnRH with longer half-lives – continuous form (Goserelin, Histrelin, Leuprolide, Nafarelin, Triptorelin)
- GnRH receptor antagonists (Ganirelix, Cetrorelix, Abarelix)

Stimulation of the Gonadal Axis by Gonadotropins

Drug Description:
- Menotropins are obtained from the urine of menopausal women and contain FSH and LH
- hCG is a placental hormone and an LH agonist
- Urofollitropin is purified FSH isolated from the urine of postmenopausal women
- Follitropin is a recombinant from of human FSH

Mechanism of Action:
- Replaces FSH and LH

Drug Indications:
- Ovulation induction (in women) in hypogonadotropic hypogonadism, polycystic ovary syndrome, obesity
- Controlled ovarian hyperstimulation in assisted reproductive technology procedures (example IVF)
- Infertility in male hypogonadotropic hypogonadism

Side Effects:
- Ovarian hyperstimulation syndrome (associated with ovarian enlargement, ascites, hydrothorax, hypovolemia, sometimes resulting in shock)
- Increase in multiple pregnancies (15-20% chance)
- Increased risk of gynecomastia in men
Contraindications:
- Any endocrine disorder other than anovulation (eg thyroid or adrenal dysfunction)
- Primary gonadal failure
- Pituitary tumors or sex-hormone dependent tumors
- Ovarian cyst or enlargement
- Pregnancy

❖ Stimulation of the Gonadal Axis by GnRH Agonist (Pulsatile)

- Pulsatile GnRH secretion or short-half life GnRH analogue Gonadorelin (half-life ~4 minutes) can stimulate the gonadotroph cells to produce and release LH and FSH (Stimulation of gonadal axis): mimicking physiology.

- Used mostly in diagnosis of hypogonadism and occasionally to stimulate ovulation or to treat infertility in men.

❖ Inhibition of the Gonadal Axis by GnRH Agonist (Sustained)

Drug Description:
- Goserelin, Histrelin, Leuprolide, Nafarelin, Triptorelin are synthetic analogs of GnRH
- More potent and longer-lasting than native GnRH or gonadorelin
- Long half-life (~3 hours)

Mechanism of Action:
- Sustained, nonpulsatile administration of GnRH or GnRH analogs with long half-life desensitizes the GnRH receptors and inhibits the release of FSH and LH in both men and women - (Inhibition of gonadal axis).

- Produces biphasic response:
  1. first there is a transient (7-10 days) increase in gonadal hormone levels (flare) – agonist effect
  2. followed by a long-lasting suppression of gonadotropins and gonadal hormones – inhibitory action

Drug Indication:
- To keep the LH surge low in controlled ovarian hyperstimulation that provides multiple mature oocytes for assisted reproductive technologies (like IVF) - [leuprolide, nafarelin]
- Endometriosis & Uterine fibroids [leuprolide, nafarelin, goserelin]
- Adjunctive in prostate cancer [leuprolide, goserelin, histrelin, triptorelin]
- Central precocious puberty [leuprolide, nafarelin]
- Others include: advanced breast & ovarian cancer, amenorrhea and infertility in women with polycystic ovary disease

Side Effects:
- Hot flashes, sweats, headache (menopausal symptoms)
- Osteoporosis
- Urogenital atrophy
- Temporary worsening of precocious puberty during the initial weeks of treatment
**Contraindications:**
- Hypersensitivity to GnRH or GnRH analogs
- Pregnancy
- Breast feeding

- Inhibition of the Gonadal Axis by GnRH receptor Antagonists

**Drug Description:**
- Ganirelix, Cetrorelix and Abarelix are used to inhibit gonadal axis
- Ganirelix and Cetrorelix produce immediate antagonistic effect, and so their duration of administration during IVF is shorter compared to GnRH agonists.

**Mechanism of Action:**
- They function as competitive antagonists of GnRH receptors
- Inhibits the secretion of FSH and LH in a dose dependent manner
- Does not produce the flare effect (increased FSH/LH) as GnRH agonists

**Drug Indications:**
- Ganirelix and Cetrorelix - keeps LH surge low in controlled ovarian hyperstimulation in IVF, resulting in improved rates of implantation and pregnancy
- Abarelix - used in metastatic prostate cancer in patients with extensive metastases or tumor encroaching on the spinal cord

**Side Effects:**
- Ovarian hyperstimulation syndrome
- QT interval prolongation (abarelix)
- Ectopic pregnancy, thrombotic disorder, spontaneous abortion (ganirelix)
- Anaphylaxis (cetrorelix)

**Contraindications:**
- Pregnancy, lactation, ovarian cysts or enlargement not due to polycystic ovarian syndrome
- Primary ovarian failure
- Thyroid or adrenal dysfunction
- Vaginal bleeding of unknown etiology

- Gonadotropin and GnRH in Assisted Reproductive Technology (IVF)
5. Hypothalamic-Pituitary-Prolactin Axis

A. Regulation of Prolactin Secretion
Lactotrophs of the anterior pituitary produce and secrete prolactin. Prolactin release is inhibited by dopamine, secreted by hypothalamus and increased by Thyrotropin-releasing hormone or TRH. Prolactin does not stimulate hormone secretion in its target organ (mammary gland) and so there is no negative feedback regulation. Increased estrogen levels during pregnancy stimulate prolactin release. Suckling provides a powerful stimulus for prolactin release.

B. Physiological Actions of Prolactin
Prolactin regulates mammary gland development, milk protein biosynthesis and secretion. Increased prolactin inhibits GnRH release and thus the hypothalamic-pituitary-gonadal axis and estrogen synthesis, thereby suppressing ovulation during lactation.

C. Disorders of Hypothalamic-Pituitary-Prolactin Axis

Features of Hyperprolactinemia
Hyperprolactinemia occurs more commonly due to prolactin secreting adenomas. Hyperprolactinemia produces
- A syndrome of amenorrhea and galactorrhea, infertility in women
- Loss of libido and infertility in men
- In large tumors it can cause visual changes due to compression of the optic nerves

Pharmacology of Hyperprolactinemia

Drugs Used:
- Dopamine Receptor Agonists Bromocriptine, Cabergoline, Pergolide; (Quinagolide is approved in Europe, not available in USA)

Prolactin Deficiency:
- No preparation of prolactin is available to treat these patients

✈ Treatment with Dopamine Receptor Agonists

Drug Description:
- Bromocriptine, Cabergoline, Pergolide, Quinagolide are synthetic dopamine receptor agonists.
- High affinity to dopamine D2 receptors

Mechanism of Action:
- They inhibit pituitary prolactin release
- GH release is reduced in patients with acromegaly, although less effectively

Drug Indication:
- Amenorrhea, galactorrhea and infertility from hyperprolactinemia, premenstrual syndrome (Bromocriptine, Cabergoline)
- Acromegaly: requires high doses, and effective only if pituitary tumor secretes both prolactin and GH; otherwise combination therapy with Octreotide is effective (Bromocriptine)
- Parkinson’s disease (Bromocriptine, Pergolide, Cabergoline)
Side Effects:
- Orthostatic hypotension
- Cerebral vascular accident, seizure, acute myocardial infarction (Bromocriptine)
- Arrhythmia, myocardial infarction, heart failure (Pergolide)
- Pulmonary fibrosis and pleural effusion (Cabergoline)

Contraindications:
- Hypersensitivity to ergot derivatives
- Uncontrolled hypertension
- Toxemia of pregnancy (Bromocriptine)
PHARMACOLOGY OF GONADAL HORMONES: ESTROGENS & PROGESTINS

Date: Friday, March 20, 2015 – 9:30 & 10:30 am
Reading Assignment: Katzung Chapter 40

KEY CONCEPTS & LEARNING OBJECTIVES

A. To describe the physiological actions and pharmacological effects of estrogens and progestins those are relevant to their clinical uses.
B. To describe the adverse effects and contraindications to use of estrogens and progestins.
C. To describe the current strategies for the use of estrogens and progestins in oral contraceptives and in hormone replacement therapy in menopause.
D. To describe pharmacological actions and clinical uses of selective Estrogen Receptor Modulators (SERMs).

Drugs/Hormones Discussed:

<table>
<thead>
<tr>
<th>Estrogens and related</th>
<th>Progestins and related</th>
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<tbody>
<tr>
<td>Estradiol</td>
<td>Norgestrel</td>
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<tr>
<td>Ethynyl estradiol</td>
<td>Etonogestrel</td>
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<tr>
<td>Conjugated equine estrogens</td>
<td>Medroxyprogesterone</td>
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<tr>
<td>Estradiol Transdermal</td>
<td>Levo-norgestrel</td>
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<tr>
<td>Diethylstibestrol/DES</td>
<td>Norethindrone</td>
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<tr>
<td>Tamoxifen, Clomiphene, Raloxifene (SERM)</td>
<td>Mifepristone (PR antagonist)</td>
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<td>Fulvestrant (ER antagonist)</td>
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<tr>
<td>Anastrozole, Letrozole, Exemestane,</td>
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<tr>
<td>Formestane (Aromatase inhibitors)</td>
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Gonadal Hormones:

- **Estrogens**
- **Progestins**
- **Androgens**

I. **ESTROGENS**: Major secretary product of ovary, also formed in the liver from estriol and also produced in peripheral tissue from androgens.

II. **PROGESTINS**: Are synthesized in the ovary, testis and adrenal from circulating cholesterol. It is also synthesized by the placenta during pregnancy.

III. **ANDROGENS**: Are synthesized mainly by testis (95%) and in adrenal glands (5%).
I. ESTROGENS: PHYSIOLOGY AND PHARMACOLOGY

Natural Estrogens:

- Estradiol 17ß (E2); most estrogenic in action.
- Estrone (E1); somewhat less estrogenic.
- Estriol (E3); not very active metabolite.

Synthetic Estrogens:

Synthetic Steroidal
- Ethinyl estradiol
- Mestranol
- Quinestrol

Synthetic Nonsteroidal
- Diethylstilbestrol
- Chlorotrianisene
- Methallenestril

Diethylstilbestrol
HYPOTHALAMIC-PITUITARY REPRODUCTION AXIS:

- GnRH (Gonadotropin-Releasing Hormone) is secreted by hypothalamus in **pulses** and travels through hypothalamic-pituitary portal system to stimulate gonadotroph cells of the anterior pituitary gland. These cells increase the synthesis and secretion of LH (Luteinizing Hormone) and FSH (Follicle-stimulating Hormone).
- In female, LH stimulates the Thecal cells to synthesize androgen, which is aromatized to estrone and estradiol in the Granulosa cells via FSH action.
- In male, LH stimulates testicular Leydig cells to increase the synthesis of Testosterone, which diffuses to neighboring Sertoli cells.
- Both Sertoli and Granulosa cells synthesize and secrete, **Inhibin A**, **Inhibin B**, and **Activin**. Inhibins inhibit the release of FSH, while Activin stimulates FSH release. Inhibins or Activin do not regulate LH release.
- In the male, testosterone works as a negative regulator of pituitary gland and hypothalamic hormone release.
- In female, estrogen’s role is more complex and can work as **positive or negative** feedback depending on the prevailing hormonal milieu.
BIOSYNTHESIS AND METABOLISM OF ESTROGENS:

BASIC MECHANISM OF STEROID HORMONE ACTION:
a) Hormone diffuses into target cell and binds to receptor in cytoplasm or nucleus.
b) Hormone-receptor complex dimerizes in nucleus and binds to specific regions on DNA; complex w/ co-activators and co-repressors.
c) Complex promotes or inhibits transcription of specific genes.

D. PHYSIOLOGICAL ACTIONS OF THE ESTROGENS:

1. Reproductive actions:
   a. Growth, development, and maintenance of primary and secondary female sex characteristics.
   b. Physiological changes at puberty and adolescence (e.g., growth, epiphyseal closure of bones).
   c. Neuroendocrine regulation of the menstrual cycle; negative feedback and positive feedback regulation of gonadotropin secretion.
   d. Stimulates growth (proliferation) of uterine endometrium.
   e. Stimulates secretion of thin cervical mucus (facilitates sperm transport).

2. Metabolic actions:
   a. Increases circulating High Density Lipoproteins (HDL), decreases low density lipoproteins (LDL).
   b. Increases cholesterol saturation of bile (thus lack of E2 leads to gallbladder stone).
   c. Increases blood pressure via increased synthesis of renin substrate.
   d. Increases synthesis of clotting factors, increased # of platelets and platelet aggregation.
   e. Decreases bone resorption; physiological role in bone remodeling.

3. Higher CNS functions:
   a. Positive effects on mood, cognition, memory.
   b. ‘Neuroprotective “effects: protective against damage from ischemia, neurodegenerative disorders.

E. PHARMACOKINETICS:

2. Well absorbed from GI tract and transdermally; substantial first pass metabolism of estrogens in liver after oral administration.
3. E2 is metabolized mainly to E1 and conjugated; E2 is more rapidly metabolized than the analogues used clinically (e.g. ethinyl E2).
4. Pharmacokinetic drug interactions:
   a. Agents that induce cytochrome P450 enzymes can enhance metabolism and Interfere w/ therapeutic actions (e.g., unwanted pregnancies). Examples: rifampin, phenytoin, carbamezepine, phenobarbital, topiramate, St. John’s Wort.
   b. Some antibiotics (penicillin, tetracycline) may reduce bioavailability by altering intestinal flora.
F. CLINICAL USES OF ESTROGENS:
   1. As a component of OC; mainly ethinyl estradiol.
   2. In HRT during menopause (Premarin ® most widely used).
   3. HRT for hypogonadism in women.
   4. Rx of dysmenorrhea, dysfunctional uterine bleeding (oligomenorrhea) and some amenorrheic states; perimenopause.
   5. Rx of delayed puberty.
   6. Rx of acne (Ortho-Tri-Cyclen ®; Estrostep ®).

F.1 ESTROGEN PREPARATIONS:

   ➢ Drug Description:
     ▪ Conjugated estrogens (e.g. Premarin).
     ▪ Estradiol (e.g. Estrace and others).
     ▪ Estradiol Transdermal (e.g. Climara, Estraderm, etc.).
     ▪ Ethinyl Estradiol.
     ▪ Diethylstilbestrol/DES (e.g. Stilphostrol).

   Drug Indication:
     ▪ Vasomotor symptoms of menopause.
     ▪ Vulvar and vaginal atrophy.
     ▪ Female hypoestrogenism secondary to hypogonadism castration or primary ovarian failure.
     ▪ In combination with other therapeutic measures to retard bone loss and osteoporosis in post-menopausal women.

   Side Effects:
     ▪ Nausea & vomiting
     ▪ Edema
     ▪ Headache
     ▪ Breast tenderness
     ▪ Venous thrombosis
     ▪ Breakthrough bleeding
     ▪ Estrogen alone (without progesterone) causes endometrial hyperplasia and possible endometrial carcinoma.
     ▪ Increased incidence of adenocarcinoma of the vagina in female offsprings of patients who have taken Diethylstilbestrol for advanced prostate cancer.

   Contraindication:
     ▪ Breast & Endometrial cancers.
     ▪ Cerebral vascular coronary artery disease.
     ▪ Benign or malignant liver tumors.
     ▪ Sever hypertension.
     ▪ Pregnancy
     ▪ Female smokers over 35 years of age.
     ▪ Thrombotic disorders.
F.2 CLINICAL USES OF SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS):

SERMS are Estrogen antagonist in some tissues and estrogen agonist in other tissues. The basis for tissue selectivity may be related to tissue-specific expression of estrogen-receptor subtypes and the differential ability of the ligand-receptor complex to recruit transcriptional co-activators and co-repressors, and differential binding of transcription factors to receptor-ligand-co-activators /co-repressors complex.

- **Drug Description:**
  - Tamoxifen

**Drug Indications:**
Tamoxifen is used for prevention, palliative and as an adjuvant therapy for breast cancer.

**Mechanism of Action:**
It acts as an estrogen receptor antagonist in breast tissue and as a partial agonist in endometrium and bone.

**Side Effects:**
- Malignant neoplasma of endometrium
- Cataract,
- Pulmonary embolism
- Hot flashes
- Abnormal menstruation
- Vaginal discharge

**Contraindication:**
- History of deep vein thrombosis or pulmonary embolism
- Pregnancy

**Therapeutic Considerations:**
- Tamoxifen administration is associated with 4-6 fold increase in the incidence of endometrial cancer.
- Administered for no more than 5 years, to minimize the risk of endometrial cancer.

- **Drug Description:**
  - Clomiphene

**Drug Indications:**
Used for female infertility due to ovulatory disorder

**Mechanism of Action:**
An estrogen receptor antagonist in hypothalamus and pituitary gland, and partial agonist in ovaries; disinhibits GnRH release and increases the level of LH and FSH. The increased FSH stimulates follicular growth, LH surge and ovulation.
Side Effects:
- Thromboembolism
- Ovarian cysts and hypertrophy
- Flushing and vasomotor symptoms
- Abdominal discomfort

Contraindication:
- Pregnancy
- Thyroid or adrenal dysfunction
- Liver disease
- Endometrial carcinoma
- Ovarian cysts
- Organic intracranial lesion

Therapeutic Considerations:
Unlike exogenous FSH, clomiphene use is rarely associated with the ovarian hyperstimulation syndrome.

Drug Description:
Raloxifene

Drug Indications:
Osteoporosis prevention and treatment

Mechanism of Action:
Estrogen receptor agonist in bone and estrogen receptor antagonist in uterus and breast

Side Effects:
- Retinal vascular occlusion
- Venous thromboembolism
- Hot flashes
- Leg cramps

Contraindication:
- Pregnancy
- History or presence of venous thromboembolism

Therapeutic Considerations:
Decreases risk of invasive breast cancer in postmenopausal women with osteoporosis
F.3 CLINICAL USE OF ESTROGEN RECEPTOR ANTAGONIST:

- **Drug Description:**
  Fulvestrant

**Drug Indications:**
Treatment of estrogen receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

**Mechanism of Action:**
Competitively inhibit estrogen binding to receptor, blocking the action of estrogen on target tissues.

**Side Effects:**
- Nausea
- Asthenia
- Pain
- Vasodilation (hot flashes)
- Headache

**Contraindication:**
Pregnancy

**Therapeutic Considerations:**
Pure estrogen receptor antagonist with no agonist activity

F.4 CLINICAL USE OF AROMATASE INHIBITORS:

- **Drug Description:**
  - Anastrozole
  - Letrozole
  - Exemestane
  - Formestane

**Drug Indications:**
Treatment and prevention of estrogen receptor positive early-stage, locally advanced, and metastatic breast cancer

**Mechanism of Action:**
Anastrozole and Letrozole are competitive inhibitors of aromatase, the enzyme that catalyzes the formation of estrogens from androgen precursors (i.e. androstenedione). Exemestane and Formestane are irreversible (covalent) inhibitors of aromatase.
Side Effects:
- Osteoporotic fractures
- Thrombophlebitis
- Hypercholesterolemia
- Profuse vaginal bleeding
- Peripheral edema
- Rash
- Nausea
- Arthralgia
- Bone pain
- Headache
- Depression
- Dyspnea

Contraindication:
Hypersensitivity to all aromatase inhibitors

Therapeutic Considerations:
- Aromatase inhibitors may be more effective than SERMs for the treatment of breast cancer.
- Extreme suppression of estrogen action could lead to high risk of osteoporotic fractures in women taking aromatase inhibitors.
II. PROGESTINS: PHYSIOLOGY AND PHARMACOLOGY
The naturally occurring progestin is progesterone. There are several synthetic progestins and they are not a uniform group of compounds. A new group of third generation of synthetic progestins has also been introduced principally as components of oral contraceptives (e.g. Desogestrel, Norethynodrel, etc).

A. PHYSIOLOGICAL ACTIONS OF PROGESTERONE:
1. Neuroendocrine regulation of the menstrual cycle; esp. negative feedback during luteal phase.
2. Transforms estrogen-primed proliferative uterine endometrium to secretory endometrium; essential for implantation of fertilized ovum ( nidation).
3. Transforms cervical mucus to thick and viscous (inhibits sperm transport).
4. Increase in body temperature (0.5-1.0° F) at ovulation and during luteal phase.
5. Essential for maintenance of pregnancy; Inhibits uterine contractility during pregnancy, and also suppresses immune responses.
7. Antagonizes some, but enhances other, actions of estrogens.

B. PHARMACOKINETICS OF PROGESTINS
Similar to the estrogens

C. CLINICAL USES OF PROGESTINS
1. As OC alone, or a component of OC.
2. In HRT during menopause (mainly medroxyprogesterone) for endometrial protection.
3. Rx of oligomenorrhea or amenorrhea.
4. Rx of polycystic ovary syndrome.
5. Rx of endometriosis.

D. PHARMACOLOGY OF ORAL CONTRACEPTIVES:
Three Major Types:
- Progestin-Only
- Combination (COCs)
- Emergency

D.1 Clinical use of Progestin-Only Contraceptives:
- **Drug Description:**
  - Norgestrel
  - Norethindrone
  - Medroxyprogesterone acetate (injectable)
  - Etonogestrel (implant)
**Drug Indications:**
Contraception

**Mechanism of Action:**
Alter frequency of GnRH pulsing and decrease anterior pituitary gland responsiveness to GnRH. Secondary mechanisms of pregnancy prevention include alterations in tubal peristalsis, endometrial receptivity, and cervical mucus secretions, which together prevent the proper transport of both egg and sperm.

**Side Effects:**
- Irregular periods
- Breast tenderness
- Nausea
- Dizziness
- Headaches

**Contraindication:**
- Acute liver disease
- Benign or malignant liver tumors
- Known or suspected breast cancer
- Pregnancy

**Therapeutic Considerations:**
During spotting, irregular and light menstrual periods: Medroxyprogesterone acetate can be given parenterally every 3 months. Etonogestrel (implant) is effective for 3 years, and Levonorgestrel (orally) can be used in case of emergency contraception.

**KEY CONCEPTS ON COCs**
COCs consist of an estrogen, usually EE, and a progestin, usually a 19-nortestosterone agent. The classic regimen is 21 days on/7 days placebo.
- Efficacy: approx. 0.1% incidence of accidental pregnancy in 1st year.
- Mechanism: primarily negative feedback on gonadotropin secretion; progestin may thicken cervical mucus.

D.2 Clinical use of Estrogen-Progestin (combination) Contraception:

- **Drug Description:**
  - **Estrogens:** Ethinyl estradiol, Mestranol
  - **Progestins:** Norgestrel, Levonorgestrel, Norethindrone, Norethindrone acetate, Ethynodiol, Norgestimate, Gestodene, Desogestrel, Drospirenone

- **Combinatin OC Examples:**
  - EE + norgestrel (Lo/Ovral 28®)
  - EE + drospirenone (Yasmin ®)

- **Drug Indications:**
  - Contraception

- **Mechanism of Action:**
  - Supress GnRH, LH and FSH secretion and follicular development, thereby inhibiting ovulation; secondary mechanisms of pregnancy prevention include alterations in tubal peristalsis, endometrial receptivity and cervical mucus secretions which together prevent the proper transport of both egg and sperm.

- **Side Effects:**
  - Arterial and venous thromboembolism
  - Pulmonary embolism
  - Cerebral thrombosis
  - Gallbladder disease
  - Hypertension
  - Hepatic neoplasm
  - Abnormal menstruation
  - Breakthrough bleeding
  - Breast tenderness
  - Bloating symptoms
  - Migraine
  - Weight change

- **Contraindication:**
  - Breast cancer
  - Endometrial cancer or estrogen-dependent neoplasm.
  - Cerebral vascular or coronary artery disease.
  - Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
  - Benign or malignant liver tumors
- Severe hypertension
- Prolonged immobilization
- Pregnancy
- Female smokers over 35 years of age
- Thrombotic disorders

**Therapeutic Considerations:**
- Progestins vary in their androgenic activity.
- Norgestrel and levonorgestrel have the highest androgenic activity.
- Norethindrone and norethindrone acetate have medium androgenic activity.
- Ethynodiol, norgestimate, gestodene and desogestrel have low androgen receptor cross-reactivity.
- Drospirenone is a synthetic progestin which has anti-androgenic activity.
- Combination estrogen-progestin contraceptives are available in various forms in the market, like oral tablets, vaginal rings, transdermal patches.
- Levonorgestrel is used as morning-after contraception.
- Lowest effective dose of ethinyl estradiol is preferred to reduce the risk of deep vein thrombosis. In a woman with uterus, estrogen is always coadministered with a progestin, to avoid risk of endometrial cancer due to estrogen alone.

**D.3 Clinical use of Progesterone Receptor Antagonist:**

- **Drug Description:**
  Mifepristone (RU-486)

**Drug Indications:**
Abortion (through day 49 of pregnancy)

**Mechanism of Action:**
Inhibits progesterone binding to receptor

**Side Effects:**
- Prolonged bleeding time
- Bacterial infections
- Sepsis
- Nausea
- Vomiting
- Diarrhea
- Cramps
- Headache

**Contraindication:**
- Chronic adrenal failure
- Ectopic pregnancy
- Hemorrhagic disorders
- Anticoagulation therapy
- Inherited porphyrias
Therapeutic Considerations:
- Commonly administered in conjunction with misoprostol, a prostaglandin analogue that stimulates uterine contractions; co-administration of misoprostol can cause nausea and vomiting.
- Higher concentration of mifepristone also blocks the glucocorticoid receptors.

D.4 EMERGENCY (morning after) CONTRACEPTION:
- Refers to use of medication to prevent unwanted pregnancy after unprotected intercourse/post-coital.
- Historically estrogen-progestin combination therapy was in practice; which was not approved by FDA.
- FDA has now approved use of two doses of “minipill” (0.75mg of levonorgestrel), separated by 12 hrs.
- Levonorgestrel is a potent progestin that can block the LH surge, disrupting normal ovulation, and produce endometrial changes for implantation.
- The first dose should be taken anytime within 72 hrs after intercourse and second dose after 12 hrs of first dose.

ADVERSE EFFECTS:
- Nausea/vomiting
- Headache
- Dizziness
- Mastalgia

SUGGESTED MECHANISMS:
- Inhibition of ovulation via strong negative feedback
- Impairment of sperm transport
- Interference w/ endometrial receptivity

D.5 HORMONE REPLACEMENT THERAPY IN MENOPAUSE:
“Menopause is not a disease, but it does have serious clinical sequel.”- R. Lobo, 1999

Physiology of Menopause: defined (retrospectively) as the last menstruation; diagnostically if one year since last menses and plasma FSH > 25 mIU/ml. Avg. age in U.S. fitting this definition: 51 yrs w/ large variation; range 40-58 years.
1. Physiological basis: exhaustion of supply of ovarian follicles, loss of cells that secrete estradiol, progesterone; estradiol reduced to castrate levels; less active estrone from conversion of androgens; removal of negative feedback elevates the gonadotropins, no cycles.
2. Perimenopause: transition to menopause, early onset of symptoms, esp. vasomotor, insomnia, mood changes, irregular cyclicity; may begin in late 30’s, early 40’s.
KEY CONCEPT: Most adverse events in menopause result from estrogen deficiency.

<table>
<thead>
<tr>
<th>Early symptoms</th>
<th>Physical changes (intermediate)</th>
<th>Disease development (Longer term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor instability (70%)</td>
<td>Urogenital atrophy (60%)</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Insomnia (55%)</td>
<td>Urinary incontinence</td>
<td>Cardiovascular disease (?)</td>
</tr>
<tr>
<td>Fatigue (90%)</td>
<td>Recurrent genital tract infection</td>
<td>Dementias (?)</td>
</tr>
<tr>
<td>Mood changes (90-95%)</td>
<td>Skin atrophy, loss of collagen</td>
<td></td>
</tr>
</tbody>
</table>

(%) reporting

Major indications for HRT in menopause:
1. vasomotor instability (hot flashes or flushes, night sweats)
2. mood changes
3. urogenital atrophy
4. prevention and Rx of osteoporosis

HRT preparations commonly used:
1. conjugated equine estrogens (Premarin®, Cenestin®), usually 0.625 mg/day, po
2. micronized estradiol (Estrace®), po
3. E2-17β in skin patch (Vivelle®)
4. Medroxyprogesterone (Provera®, Cycrin®), po
5. Combination products: Prempro®, Premphase®: Premarin® plus Cycrin®, po
   - CombiPatch®: transdermal E2-17β plus norethindrone

Effects of HRT:
1. Relief from vasomotor symptoms; urogenital atrophy and recurrent urinary symptoms
2. Relief from fatigue, depression
3. Maintenance of bone mineral density

Common adverse effects of HRT:

KEY CONCEPTS: Biological activities of estrogens used in HRT are generally lower than in OCs. The absolute and relative contraindications to estrogen use are similar to those for OCs.
1. estrogen component assoc w/ nausea, mastalgia, headache, fluid retention
2. progestin component assoc w/ weight gain, headache
HRT and Cancer:

1. **Endometrial cancer**: Unopposed estrogen taken for 5 years increases the risk of endometrial hyperplasia and cancer by 5-fold, and by 8-fold if taken for longer than 5 years. Risk is nearly eliminated by addition of progestin.

2. **Breast Cancer**:
   a. Little or no increased risk for HRT < 5 yrs
   b. Women’s Health Initiative reports relative risk (RR) of 1.26 for approx. 5 years of HRT, and perhaps decreased with ERT
   c. HRT for 10-15 yrs RR ~1.3, from U.S. studies
   d. Results from the Million Women Study (UK) (see Lancet 362: 414-427, 2003):

   1. Overall relative risk for breast cancer incidence in current users vs. never-users was 1.66.
   2. Overall relative risk of breast cancer death was 1.22, same comparison.
   3. Risk increase with duration of use.
   4. No risk for past users.
   5. Risk was higher in estrogen+progestin vs. estrogen alone; Progestin component now believed to contribute significantly.
   6. No differences continuous v. sequential regimens or specific compounds; no difference oral vs. transdermal.
PHARMACOLOGY OF GONADAL HORMONES: ANDROGENS

Date: Tuesday, March 23, 2015 – 10:30 am
Reading Assignment: Katzung Chapter 40

KEY CONCEPTS & LEARNING OBJECTIVES

A. To describe the physiological actions, pharmacological effects, and clinical uses of androgens.
B. To describe the adverse effects and contraindications to use of androgens.
C. To discuss the pharmacology and clinical uses of androgen antagonists.

Drugs/Hormones Discussed:

<table>
<thead>
<tr>
<th>Androgens and related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
</tr>
<tr>
<td>Methyltestosterone</td>
</tr>
<tr>
<td>17α-ethinyltestosterone (Danazol)</td>
</tr>
<tr>
<td>Finasteride (inhibitor of DHT conversion)</td>
</tr>
<tr>
<td>Flutamide, Spironolactone (AR antagonist)</td>
</tr>
</tbody>
</table>

Gonadal Hormones:
- Estrogens
- Progestins
- **Androgens**

III. ANDROGENS: PHYSIOLOGY AND PHARMACOLOGY

NATURAL ANDROGENS:
- Testosterone
- Dihydrotestosterone (DHT)
- Androstenedione
- Dehydroepiandrosterone (DHEA)

SYNTHETIC ANDROGENS: Many
A. ANDROGEN SYNTHESIS:

B. BASIC MECHANISM OF ACTION OF ANDROGENS:
1. Testosterone diffuses into cell and binds to intracellular androgen receptor OR is converted to dihydrotestosterone, which binds to androgen receptor, OR is converted to estradiol, which binds to estrogen receptor.
2. Hormone-receptor complex dimerizes in cell nucleus and binds to specific hormone-response elements on DNA, along with a complex of co-activator or co-repressor proteins.
3. This promotes or inhibits transcription of specific genes, resulting in physiologic effect.

C. PHYSIOLOGICAL ACTIONS OF ANDROGENS:
1. Reproductive actions:
   a. Growth, development and maintenance of primary (genitalia and genital tract) and secondary sex characteristics in men.
   b. Early stages of breast and pubertal development in girls (adrenarche).
   c. Promote spermatogenesis (with FSH).
   d. Neuroendocrine regulation of gonadotropin secretion.
   e. Stimulate libido.

2. Anabolic actions:
   a. Increase protein synthesis, increased lean body mass, and body growth.

3. Effects on growth:
   a. Skeletal growth and closure of epiphyses of long bones during puberty and adolescence.
   b. Growth of larynx and voice deepening at puberty
4. **Metabolic/hematologic actions:**
   a. Erythropoiesis
   b. Decreased synthesis of several clotting factors
   c. Increased sebum production in skin
   d. Decrease synthesis of HDL cholesterol, increase synthesis of LDL-cholesterol
   e. Androgenic alopecia (male pattern baldness)
   f. Increases bone density

D. **THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN MALES:**
1. T secreted from interstitial (Leydig) cells exerts negative feedback on hypothalamus and pituitary to inhibit LH secretion.
2. T exerts paracrine effects in the seminiferous tubules along with FSH to promote Spermatogenesis.
3. Inhibin secreted from Sertoli cells (support cells within the tubules for spermatogenesis) exerts selective inhibition over FSH secretion.
E. CONSEQUENCES OF ANDROGEN DEFICIENCY IN MEN:
1. Decreased libido; erectile dysfunction
2. Decreased lean muscle mass; increased adipose tissue mass
3. Decreased axillary and pubic hair
4. Anemia
5. Osteoporosis
6. Decreased energy, sense of well being

F. THERAPEUTIC USES OF ANDROGENS:
- HRT in primary or secondary hypogonadism
- Induction of puberty in delayed maturation
- Rx of osteoporosis in males

F.1 Clinical use of Androgens in HRT:

- Drug Description:
  - Testosterone enanthate
  - Testosterone cypionate

Drug Indications:
Hypogonadism

Mechanism of Action:
- Replacement of testosterone produces androgenic effects, such as:
  a) Growth and maturation of prostate
  b) Seminal vesicles
  c) Penis & Scrotum
  d) Development of male hair distribution
  e) Laryngeal enlargement
  f) Vocal cord thickening
  g) Alterations in body musculature, and
  h) Fat distribution

Side Effects:
- Cholestatic jaundice syndrome
- Liver carcinoma
- Benign prostatic hyperplasia
- Prostate cancer
- Gynecomastia
- Acne
- Headache

Contraindication:
- Breast cancer in men
- Prostate cancer
- Pregnancy when used in women
**Therapeutic Considerations:**
- Various delivery routes and formulations available: intramuscular, transdermal, topical gel and oral. The transdermal is preferred to prevent first-pass hepatic metabolism.
- Androgen HRT for men with consistent symptoms of hypogonadism.

**F.2 Clinical uses of Androgen Receptor Antagonists:**

- **Drug Description:** Flutamide

**Drug Indications:**
- Metastatic prostate cancer
- Benign prostatic hypertrophy

**Mechanism of Action:**
Competitive inhibition of dihydrotestosterone & testosterone binding to the receptor.

**Side Effects:**
- Hepatotoxicity
- Hematopoietic disorders
- Diarrhea
- Nausea
- Rash
- Hot Flashes

**Contraindication:**
Severe hepatic impairment

**Therapeutic Considerations:**
- Flutamide is comparatively better than DES and leuprolide in treatment of prostate cancer.
- Excellently effective when combined with medical or surgical castration.

**F.3 Clinical uses of Androgen Receptor Antagonists:**

- **Drug Description:** Spironolactone

**Drug Indications:**
- Hirsutism
- Hypertension
- Acne vulgaris
- Edema associated with heart failure
- Cirrhosis or nephrotic syndrome
- Hypokalemia
- Primary aldosteronism
Mechanism of Action:
Competitive inhibition of dihydrotestosterone & testosterone binding to the receptor

Side Effects:
- Gastrointestinal hemorrhage
- Hyperkalemic metabolic acidosis
- Agranulocytosis systemic lupus erythematosus
- Gynecomastia
- Dyspepsia
- Lethargy
- Abnormal menstruation
- Impotence
- Rash
- Breast cancer – not yet established

Contraindication:
- Anuria
- Hyperkalemia
- Acute renal insufficiency

Therapeutic Considerations:
An aldosterone receptor antagonist but also acts as an androgen receptor antagonist.

F.4 Clinical use of Inhibitors of Peripheral Testosterone Conversion to DHT:

Drug Description:
Finasteride

Drug Indications:
- Benign prostatic hyperplasia
- Androgenic alopecia

Mechanism of Action:
Selective inhibition of type II 5 α-reductase, the enzyme responsible for conversion of testosterone to dihydrotestosterone in prostate, liver & skin.

Side Effects:
- Neoplasm of male breast (rare and not yet investigated)
- Breast tenderness
- Decreased libido
- Erectile dysfunction
- Ejaculatory disorder

Contraindication:
- Known or suspected pregnancy
Women and children

**Therapeutic Considerations:**

- Improves urine flow
- Can be used as alternative to transurethral resection of prostate (TRUP).
- Upto 25% reduction in prostate size when consistently used for one year.
- Most effective in patients with large prostates.
- Women should not be treated with finasteride.
Drugs used to treat Diabetes I and II

Date: Diabetes I/II  Wednesday, March 25, 2015  9:30-11:30am

Optional reading assignments: ACP Medicine (Scientific American)
Chapter 9, Sections I and II
Available via the library e-book collection
- nice background on Pathophysiology and Treatment of both type 1 and type 2 diabetes
- http://www.acpmedicine.com/cgi-bin/publiccgi.pl?loginOP

Other resources: http://www.endotext.org/
- An excellent web site that provides a series of detailed chapters on all aspects of endocrinology
- Superb resource for further reading

Key Concepts and Learning Objectives
1. Describe the fundamental differences between type 1 and type 2-diabetes.

2. List the current diagnostic criteria and therapeutic goals for the treatment of diabetes.

3. Explain the pharmacological differences between the various insulin formulations used in the treatment of diabetes, especially their duration of action and how this affects their influence on the control of postprandial glucose levels versus fasting glucose levels.

4. Explain the biological effects of insulin therapy on muscle, liver and adipose tissue

5. Discuss the relative benefits and disadvantages between a conventional and intensive insulin therapy regimen.

6. Identify the major adverse effects of insulin therapy and the therapeutic approaches to treat this condition

7. List the indications, contraindications and clinical uses for each of the major classes of hypoglycemic agents used in the treatment of type-2 diabetes.

8. Describe the mechanism of action and physiological effects of each of the major classes of hypoglycemic agents, especially their effects on fasting versus post-prandial glucose levels.

9. List the major adverse effects associated with each of the major classes of hypoglycemic agents

10. Discuss the use of combination hypoglycemic drug therapy including the use of insulin in the treatment of type-2 diabetes

11. Apply your knowledge of the pharmacology of the major classes of hypoglycemic drug agents to select the most appropriate medication for a specific patient based upon patient-specific criteria
Drugs to be covered in this lecture:

1. **Insulin Formulations**
   - **Rapid acting insulin**
     - Insulin aspart (Novolog®)
     - Insulin lispro (Humalog®)
     - Insulin glulisine (Apidra®)
   - **Regular Insulin**
     - Regular Insulin (Humulin R®, Novolin R®)
   - **Intermediate-acting insulin**
     - NPH Insulin (Humulin N®, Novolin N®)
   - **Long-lasting insulin**
     - Insulin detmir (Levemir®)
     - Insulin glargine (Lantus®)

2. **INSULIN SECRETAGOGUES**
   - **SULFONYLUREAS**
     - **1st Generation:**
       - Chlorpropamide (Diabinese®), Tolbutamide
     - **2nd Generation:**
       - Glimepiride (Amaryl®), Glyburide (DiaBeta®, Micronase®), Glipizide (Glucotrol®)
   - **MEGLITINIDES**
     - Repaglinide (Prandin®)
     - Nateglinide (Starlix®)

3. **INSULIN SENSITIZERS**
   - **BIGUANIDES**
     - Metformin (Glucophage®)
   - **THIAZOLIDINEDIONES**
     - Pioglitazone (Actos®), Rosiglitazone (Avandia®)

4. **Incretin mimetics/modulators**
   - Exenatide (Byetta®)
   - Liraglutide (Victoza®)
   - Sitagliptin (Januvia®)
   - Saxagliptin (Onglyza®)

5. **INHIBITORS OF CARBOHYDRATE DIGESTION**
   - **ALPHA-GLUCOSIDASE INHIBITORS**
     - Acarbose (Precose®)
     - Miglitol (Glyset®)
   - **SGLT2 inhibitors**
     - Canagliflozin (Invokana®)
     - Dapagliflozin (Farxiga®)

6. **Bromocriptine (Cycloset®)**

7. **Bile acid binding resin**
   - Colesevelam (Welchol®)

9. **Amylin homolog**
   - Pramlintide (Symlin®)
1. **DIABETES MELLITUS**

a) Diabetes Mellitus is a metabolic disorder that is characterized by hyperglycemia caused by either a defect in insulin production, insulin action, or a combination of the two.

b) Chronic hyperglycemia is associated with long-term damage, dysfunction and failure of various organs including the eyes, kidneys, nerves, heart and blood vessels.

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Defect</strong></td>
<td>Autoimmune destruction of pancreatic beta cells</td>
<td>Insulin resistance with progressive loss of pancreatic beta cell function</td>
</tr>
<tr>
<td><strong>Insulin levels</strong></td>
<td>zero</td>
<td>Typically higher than normal</td>
</tr>
<tr>
<td><strong>Insulin resistance</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>Typically &lt; 30yrs</td>
<td>Typically &gt; 40yrs</td>
</tr>
<tr>
<td><strong>Nutritional status at time of onset</strong></td>
<td>Undernourished</td>
<td>Typically obese</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>10-20%</td>
<td>80-90%</td>
</tr>
<tr>
<td><strong>Genetic predisposition</strong></td>
<td>moderate</td>
<td>strong</td>
</tr>
<tr>
<td><strong>Acute complications</strong></td>
<td>Ketoacidosis/wasting</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td><strong>Chronic complications</strong></td>
<td>Neuropathy, Retinopathy, Nephropathy, CVD, Peripheral vascular disease, Lower extremity amputations</td>
<td>Same as type 1</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Insulin replacement</td>
<td>Oral hypoglycemics/insulin</td>
</tr>
</tbody>
</table>

**Regulation of glucose levels during homeostasis and Diabetes**

[Diagram showing glucose regulation and diabetes pathways]
2. DIAGNOSIS AND GOALS OF DIABETES THERAPY

Symptoms of diabetes: polyuria, polydipsia, unexplained weight loss + polyphagia, blurred vision, and a causal plasma glucose concentration > 200mg/dL or FPG of > 126mg/dL.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-diabetes IFG/IGT</th>
<th>Diabetes</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>&lt;100 mg/dL</td>
<td>100-125 mg/dL</td>
<td>&gt;126 mg/dL</td>
<td>90-130 mg/dL</td>
</tr>
<tr>
<td>2hr Peak postprandial plasma glucose</td>
<td>&lt;140 mg/dL</td>
<td>140-199 mg/dL</td>
<td>&gt;200 mg/dL</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Glycated hemoglobin (HbA1c)</td>
<td>&lt;6.0%</td>
<td></td>
<td>&gt;7.0%</td>
<td>&lt;7.0%</td>
</tr>
</tbody>
</table>

Treatment Goals: To achieve and maintain glycemic levels as close to the non-diabetic range as possible in order to prevent the development of complications of chronic diabetes.

3. DRUGS TO TREAT TYPE 1 DIABETES

Insulin

a) Insulin replacement therapy is the only treatment available for patients with type 1-diabetes.

b) Commercially available insulin preparations are available in a variety of formulations that differ based upon their time of onset, peak activity and duration of action.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>5-15 mins</td>
<td>45-75 mins</td>
<td>2-4 hrs</td>
<td>For meals or acute Hyperglycemia; Can be injected immediately before meals</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Insulin</td>
<td>30-60 mins</td>
<td>2-4 hrs</td>
<td>6-8 hrs</td>
<td>For meals or acute Hyperglycemia; Needs to be injected 30-45 mins prior to meal</td>
</tr>
<tr>
<td>NPH Insulin</td>
<td>1.5-2 hrs</td>
<td>6-10 hrs</td>
<td>16-24 hrs</td>
<td>Provides basal insulin And overnight coverage</td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>~2 hrs</td>
<td>No Peak</td>
<td>20-&gt;24 hrs</td>
<td>Provides basal insulin And overnight coverage</td>
</tr>
<tr>
<td>Insulin detmir</td>
<td>~2 hrs</td>
<td>No Peak</td>
<td>6-24 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of Action.

a) Insulin acts through its plasma membrane cell surface receptor

b) Insulin corrects hyperglycemia by:
   (i) promoting glucose uptake in muscle, liver and adipose
   (ii) inhibiting hepatic glucose production (gluconeogenesis/glycogenolysis)
   (iii) inhibiting the flow of gluconeogenic precursors from muscle/adipose to the liver
   (iv) inhibiting the secretion of the counter-regulatory hormone glucagon

Insulin Administration

a) Subcutaneous injection with syringe: upper arms, upper legs, abdomen (most effective), and buttocks-sites of injection should be rotated to avoid injection site lipodystrophy
   - Initial dose 0.2-0.6 units/kg/day in divided doses
Typically 50-75% of dose is given as intermediate/long-acting insulin and the remainder is administered as rapid-acting or short acting insulin at meal times

b) Continuous subcutaneous insulin pump (regular insulin or rapid-acting insulin)
c) Inhaled Insulin (Exubera®; powder formulation of rapid-acting insulin)
   - As effective as regular insulin in type 1 and type 2 diabetes
   - NOW DISCONTINUED due to poor patient adoption

Adverse reactions
Hypoglycemia, tachycardia, fatigue, mental confusion, Injection site lipodystrophy, diapheresis, and hypersensitivity (less common with human insulin).

Drug Interactions.
   a) Drugs which DECREASE hypoglycemic effect of insulin: oral contraceptives, corticosteroids, diltiazem, niacin, ephinephrine, thiazide diuretics, Ca2+ channel blocker, beta2-adrenergic agonists and HIV protease inhibitors.
   b) Drugs that INCREASE hypoglycemic effect of insulin: alcohol, beta-blockers, salicylates, lithium, sulfonamides and tetracyclines

Hypoglycemia
a) Blood glucose levels < 60 mg/dL
b) Potentially fatal if not promptly treated
c) Caused by lack of glucose availability to the brain and CNS

Symptoms
*Mild Hypoglycemia*: Tremor, palpitations, sweating and intense hunger

*Moderate hypoglycemia*: Headache, mood changes and irritability, decreased attention, drowsiness, Patients may require assistance to help themselves
   Treatment- oral dose of a simple carbohydrate

*Severe hypoglycemia*: Unresponsiveness, Unconsciousness, convulsions, prolonged severe hypoglycemia can result in death, patients require assistance.
   Treatment. Either IV glucose or IV/IM GLUCAGON (stimulates release of glucose from liver.

Insulin Therapy Regimens
Goal - To achieve near normoglycemia, which has been demonstrated in clinical trials to prevent and/or slow the onset of diabetic complications
- Achieving normoglycemia requires the administration of multiple doses of insulin every day

**Glycemic Goals:**
- Fasting blood glucose: 90-120 mg/dL
- 2hr Postprandial BG: <180 mg/dL
- HbA1c: <7%

**Typical Insulin dose:** 0.5-0.8 units/kg/day in a divided dose split between a basla insulin (50-75% of total) and pre-prandial insulin
(A) Conventional Insulin Therapy
   a) A simple non-physiological insulin regime consisting of either a single or two daily
      injections of insulin usually a mixture of regular or rapid acting insulin together with
      intermediate (i.e. NPH) insulin given in fixed amounts in the
      same syringe before breakfast and dinner
   b) Convenient, but will not
      adequately control glycemia
   c) NOT recommended unless
      patient cannot or will not comply
      with an intensive insulin regime

(B) Intensive Insulin Therapy/Standard insulin therapy
   a) Aims to provide a more physiological profile of insulin by administration of a basal level
      of insulin to lower fasting glucose (provided by daily or twice daily injections of long-
      acting insulin preparations e.g. NPH or glargine) together with pre-meal boluses of a
      rapid or very rapid acting insulin to control postprandial glucose elevations
   b) The dose of the pre-meal bolus is
      determined by the ambient blood glucose
      level before the meal, the size and
      composition of the meal and anticipated
      activity levels.
   c) Essentially near normal glycemia can be
      achieved using an intensive insulin regime
   d) Significantly reduces the risk of diabetic
      complications
   e) Recommended for the majority of type-1
      patients

Drawbacks to intensive insulin therapy
   a) Greater effort required by patient
   b) Incidence of hypoglycemia/coma is higher
   c) Weight gain more likely
   d) Cost (~3x conventional therapy)

4. DRUGS TO TREAT TYPE 2 DIABETES

4.1 ORAL ANTI-DIABETIC DRUGS- INSULIN SENSITIZERS
4.1.1 BIGUANIDES
Metformin (Glucophage®)

4.1.1A DESCRIPTION
   a) An oral anti-hyperglycemic medication that acts to lower plasma glucose levels primarily
      by reducing hepatic glucose production.
   b) Does NOT act by promoting insulin production
   c) Recommended by ADA and EASD as first line treatment for type 2 diabetes
      concurrent with lifestyle changes, diet and exercise
4.1.1B MECHANISM OF ACTION

a) Reduces hepatic glucose production by inhibiting both gluconeogenesis and glycogenolysis
b) Increases peripheral glucose uptake and utilization in muscle and fat tissues
c) Effective only in the presence of insulin
d) Acts by inhibiting complex I in the electron transfer chain of mitochondrion resulting in an increase in the cellular concentration of AMP that in turn:
   (i) Inhibits GLUCAGON-induced hepatogluconeogenesis by inhibiting the glucagon-induced activation of adenylate cyclase
   (ii) activates the AMP-dependent protein kinase (AMPK), an important metabolic enzyme involved in cellular and systemic energy homeostasis.
       - Activation of AMPK in muscle and adipose tissue promotes glucose uptake
       - Activation of AMPK in the liver inhibits hepatic glucose production, as well as inhibiting hepatic cholesterol and triglyceride biosynthesis (potentially explains favorable effects of metformin on lipid profiles and the development of CVD- see below).
       - AMPK activation promotes fatty acid oxidation, thereby reducing FFA stores that contribute towards the development of insulin resistance
       - AMPK activity inhibits the activity of inhibitors of the insulin signaling pathway thereby enhancing insulin signaling and preventing insulin resistance.

4.1.1C INDICATIONS AND CLINICAL USE

b) Approved for either monotherapy, or in combination with other oral hypoglycemic drugs, for the treatment/prevention of hyperglycemia in type 2-diabetes.
c) Metformin is rapidly absorbed from the small intestine, it is not metabolized and is secreted in the urine with a half life of 1.5-5 hrs. Peak plasma concentration is achieved in 2 hrs & the duration of its biological effect is ~ 6hrs
d) Primarily affects fasting blood glucose levels (i.e. inhibition of hepatic gluconeogenesis) rather than postprandial glucose increases.
e) Lowers fasting blood glucose by 20% and HbA1c by ~1.5% points
f) Does NOT cause WEIGHT GAIN and can even promote WEIGHT LOSS
g) Does NOT cause HYPOGLYCEMIA
h) Multiple clinical trials show that metformin treatment DECREASES the frequency of MI, diabetes-related death and all-cause mortality in type-2 obese patients compared to other oral hypoglycemic agents
i) Potential beneficial effect on CVD outcomes likely due to the effects of metformin on improving lipid profiles- decreased TG and FFA, small decrease in LDL, modest increase in HDL

4.1.1D ADVERSE EFFECTS
a) Generally well tolerated - only ~5% of patients discontinue due to adverse effects
b) Most common adverse effect is on the GI tract- metallic taste, nausea, diarrhea and abdominal pain, which are minimized by taking the drug with food.
c) Decreases absorption of Vitamin B12, although rarely causes megalobalstic anemia
d) Lactic Acidosis is a rare (<1:100,000), but potentially fatal complication
   • Most associated with use in high risk patients- esp RENAL INSUFFICIENCY
   • Symptoms- deep/rapid breathing, vomiting, abdominal pain, muscle weakness
   • Caused by a build up of lactate in the blood due to the fact that lactate is a substrate for hepatic gluconeogenesis, which is inhibited by metformin.
   • In normal circumstances lactate is cleared by the kidney, but in renal insufficiency the lactate levels increase causing acidification of the blood

N.B. phenformin an earlier biguanide was removed from the market because of increased frequency of lactic acidosis

4.1.1E CONTRAINDICATIONS
a) Women who are pregnant or that are lactating (insulin is the preferred treatment)
b) Impaired renal function, since both metformin and lactate are entirely cleared by the kidney and patients with decreased renal function are more susceptible to drug accumulation and lactic acidosis
c) Not to be given to the elderly >80 yrs due to renal insufficiency
d) Should be discontinued in patients injected with iodinated contrast agents for radiographic studies and not started until 48hrs later to avoid contrast-induced acute renal failure which can increase metformin levels- insulin used during this time period to control hyperglycemia
e) Conditions pre-disposing to lactic acidosis:
   - Congestive heart failure requiring drug therapy
   - Myocardial Infarction- immediate withdrawal
   - Impaired liver function/excessive alcohol consumption
   - Impaired renal function
   - Shock/septicemia
   - Serious acute illness or hypoxic condition
   - Hypoxic or ischemic states i.e. lung disease

4.1.2 THIAZOLIDINEDIONES
Pioglitazone (Actos®)
Rosiglitazone (Avandia®)
4.1.2A DESCRIPTION
“Insulin Sensitizers” that increase the sensitivity of adipose tissue, skeletal muscle and liver to endogenous insulin

4.1.2B MECHANISM OF ACTION
Thiazolidinediones act as agonists of the peroxisome proliferators-activated receptor gamma (PPARγ) transcription factor, which influences the expression of multiple genes involved in the regulation of insulin sensitivity.

**Thiazolidinedione-induced activation of PPARγ increases systemic insulin sensitivity**

Activation of PPARγ results in the:
(i) Increased expression of GLUT4- the insulin-sensitive glucose transporter
(ii) Increased expression of Adiponectin- an adipocytokine involved in promoting systemic insulin sensitivity
(iii) Increased expression of genes involved in FFA uptake and FFA oxidation, which acts to decrease serum FFA that has been implicated in promoting insulin resistance.
(iv) Decreased expression of the TNF-alpha cytokine involved in promoting insulin resistance
(v) Decreased expression of Resistin an adipocytokine involved in inhibiting systemic insulin sensitivity
(vi) Remodels adipose tissue: Reduces insulin-resistant visceral adipose tissue and increases the appearance of newly differentiated insulin-sensitive subcutaneous adipocytes.
(vii) Inhibits hepatic genes involved in gluconeogenesis

*Overall these effects act to improve systemic insulin sensitivity and lower plasma glucose levels.*

4.1.2C INDICATIONS AND CLINICAL USE
a) Approved for monotherapy or in combination with either metformin, sulfonylureas or insulin in the treatment of hyperglycemia in type 2-diabetes.
b) Typically decreases FPG with moderate effect on postprandial glucose

c) Decrease Hb1Ac by 0.5-1.4% points

d) Takes 6-14 weeks to achieve maximum effect

4.1.2D ADVERSE EFFECTS

a) Weight gain – mainly subcutaneous not visceral

b) Fluid retention resulting in peripheral edema
   - Fluid retention is more common with concurrent insulin use
   - Fluid retention caused by increased expression of gamma subunit of Na+ channel in the collecting tubule cells of the nephron leading to increased Na+ reabsorption
   - Maybe related to increased risk of heart failure – BLACK BOX WARNING

c) Increased risk of bone fractures in women

4.1.2E CONTRAINDICATIONS

a) Should be used cautiously in patients with underlying liver disease- 1st
   Thiazolidinedione drug Troglitazone was removed from market due to increased fatalities due to liver failure

b) Heart Failure- should not be given to patients with Class III/Class IV cardiac disease

c) Not recommended for pregnancy (Insulin is preferred therapy)

4.2 ORAL ANTI-DIABETIC DRUGS: INSULIN SECRETAGOGUES

4.2.1 SULFONYLUREAS- INSULIN SECRETAGOGUES

1st Generation: 2nd Generation:
Chlorpropamide (Diabinese®), Glimepiride (Amaryl®)
Tolbutamide Glipizide (Glucotrol®)
Glyburide (DiaBeta®, Micronase®)

4.2.1A DESCRIPTION
Insulin secretagogues that rapidly lower blood glucose levels by promoting insulin secretion from the beta cells of the pancreas.

4.2.1B MECHANISM OF ACTION
Sulfonylureas act by interacting with the SUR1 subunit of ATP-sensitive K+ channels (Kir6.2) expressed on pancreatic beta cells, this inhibits channel activity resulting in cell depolarization that triggers voltage-gated Ca2+-channels leading to Ca2+ influx and the secretion of insulin.
4.2.1C INDICATIONS AND CLINICAL USE
   a) For control of blood glucose levels in type 2 diabetes
   b) Primarily reduce FPG, with little effect on postprandial glucose increases
   c) Decreases blood glucose by ~20% and HbA1c by ~1.5% points
   d) Approved for either monotherapy or in combination with other oral hypoglycemic drugs
   e) Typically given once per day
   f) Most effective in patients who have had diabetes for less than 10 years, whose weight is normal or slightly elevated and that can still secrete considerable amounts of insulin
   g) During the chronic progression of diabetes, as the total number of beta cells decrease, the sulfonylureas become less effective.
   h) 2nd generation drugs are more potent than 1st generation drugs, are associated with a lower frequency of inducing hypoglycemia and have fewer drug interactions.
   i) 2nd generation drugs are similar to each other in efficacy, but differ in dosage and duration of action

4.2.1D ADVERSE EFFECTS
   a) Modest weight gain (~2 kg) – primarily subcutaneous adipose tissue not visceral
   b) Can cause hypoglycemia- especially in elderly patients with impaired RENAL and/or HEPATIC function- all drugs metabolized in liver and secreted in urine
   c) Severe hypoglycemia is rare

4.2.1E CONTRAINDICATIONS
   a) Elderly Patients – lack of awareness of hypoglycemia
   b) Patients with sulfa allergies
   c) Patients with type 1-diabetes
   d) Pregnant or lactating patients (Insulin is the preferred medication)
   e) Impaired RENAL/LIVER function – all sulfonylureas metabolized in the liver and metabolites are excreted in the urine.
      Note: Glipizide is a short acting sulfonylurea that is metabolized in the liver and is excreted in the urine as inactive metabolites- it is therefore the drug of choice in the elderly or patients with chronic renal failure

4.2.1F DRUG INTERACTIONS
Sulfonylureas are highly protein bound and therefore interact with many drugs e.g. salicylates, beta-blockers, warfarin & phenylbutazone, which compete for binding and act to increase serum concentrations of sulfonylureas thereby resulting in increased potential for hypoglycemia

4.2.2 MEGLITINIDES: NON-SULFONYLUREA INSULIN SECRETAGOGUES
Repaglinide (Prandin®) and Nateglinide (Starlix®)

4.2.2A DESCRIPTION
Short acting glucose-lowering drugs that are structurally distinct from the sulfonylureas, but act similarly to lower blood glucose levels by promoting insulin secretion.
4.2.2B MECHANISM OF ACTION
Meglitinides trigger insulin secretion by a similar mechanism to the sulfonylureas, but interact with a different region of the SUR1 subunit of the beta cell ATP-sensitive K+ channel.

4.2.2C INDICATIONS AND CLINICAL USE
a) Meglitinides are short-acting glucose-lowering drugs used for the treatment of hyperglycemia in type 2 diabetes.
b) Both drugs are rapidly absorbed and their peak action is at 1 hr and lasts for 4 hrs, they must therefore be given frequently, typically three times per day with meals. If meal is missed drug should be omitted.
c) Primarily affect postprandial glucose elevations with less effect on FPG.
d) Likely to be beneficial to patients with barely elevated FPG but prominent postprandial hyperglycemia.
e) Monotherapy is indicated early in type-2 diabetes when FPG is not greatly elevated.
f) They decrease Hb1Ac by ~1-1.5% points.
g) Approved for either monotherapy, or together with metformin and/or a thiazolidinedione.
h) Nateglinide is less effective than repaglinide, which is as effective as sulfonylureas or metformin at lowering Hb1Ac.
i) Considerably more expensive than sulfonylureas (~5-8X).
j) Useful as a replacement for sulfonylureas in patients with sulfa allergies.
k) Repaglinide is metabolized to inactive metabolites and is therefore safe to use in patients with renal insufficiency.

4.2.2D ADVERSE EFFECTS
a) Weight gain – similar to sulfonylureas.
b) Hypoglycemia – although less frequent than with sulfonylureas.

4.2.2E CONTRAINDICATIONS
a) Liver disease - both drugs are metabolized primarily in the liver and excreted in the bile – increased risk of hypoglycemia.
b) Not to be used during pregnancy.
4.3 INCRETIN MIMETICS AND MODULATORS

4.3.1 GLP-1 ANALOGS
Exenatide (Byetta®); Liraglutide (Victoza®)

4.3.1A DESCRIPTION
a) Exenatide is a stable analog of Glucagon-like peptide-1 (GLP-1) that binds to the GLP-1 receptor on the pancreatic beta cells and potentiates glucose-mediated insulin secretion.
b) GLP-1 is produced by the L-cells of the small intestine and helps mediate the INCRETIN EFFECT on plasma insulin levels.
c) Incretin Effect: Observation that plasma insulin levels are higher in response to oral glucose compared to intravenous glucose- indicating that factors produced in the GI tract (i.e. GLP-1) influence insulin secretion.

4.3.1B MECHANISM OF ACTION
a) Exenatide potentiates glucose-induced insulin secretion when glucose levels are high.
b) As glucose levels fall, the enhancing effects of exenatide on insulin secretion diminishes.
c) Suppresses pancreatic production of glucagon.
d) Suppresses glucose release from liver.
e) Slows stomach emptying.
f) Increases satiety.
g) Acts to maintain beta cell mass.

4.3.1C INDICATIONS AND CLINICAL USE
a) Exenatide and Liraglutide are approved as an alternative to starting insulin therapy in type 2 diabetic patients who have not achieved adequate glycemic control with either metformin, a sulfonylurea, or both.
b) Need to be injected once or twice daily.
c) Mainly acts by reducing postprandial glucose concentrations.
d) Decreases Hb1Ac by ~0.5-1% point.
e) Little risk of hypoglycemia as the enhancing effects of exenatide on insulin secretion diminish as glucose levels fall.
f) Do NOT cause WEIGHT GAIN and may cause WEIGHT LOSS.

4.3.1D ADVERSE EFFECTS
a) Frequent (30-45%) Nausea vomiting, diarrhea.
b) Increased risk of mild to moderate hypoglycemia when used with a sulfonylurea.
4.3.1E DRUG INTERACTIONS
Due to the slowing of gastric emptying it can affect the absorption of other orally administered drugs (e.g. contraceptives & antibiotics), which should be taken 1 hr before or 2 hrs after.

4.3.2 DIPEPTIDYL PEPTIDASE-IV (DPP-IV) INHIBITORS
Sitagliptin (Januvia®); Saxagliptin (Onglyza®)

DESCRIPTION
a) Sitagliptin is an inhibitor of DPP-IV, the peptidase that cleaves and inactivates GLP-1
b) Sitagliptin therefore promotes the action of endogenous GLP-1 by increasing its half-life
c) Sitagliptin is an oral medication that is taken once daily.
d) It is rapidly absorbed, reaches a peak 1-4 hrs after ingestion and is effective over 24hrs.
e) Sitagliptin can decrease both FPG and postprandial glucose elevations, although is less effective than either pramlintide or exenatide in limiting postprandial hyperglycemia
f) Stagliptin is approved for adjunct therapy of type-2 diabetes in combination with either metformin or a thiazolidinedione
g) It reduce Hb1Ac almost as effectively as exenatide i.e. 0.6-0.8%
h) There is no effect on weight loss
i) It is not associated with hypoglycemia

4.4 ORAL ANTI-DIABETIC DRUGS: INHIBITORS OF CARBOHYDRATE DIGESTION

4.4.1 ALPHA-GLUCOSIDASE INHIBITORS
Acarbose (Precose®) and Miglitol (Glyset®)

4.4.1A DESCRIPTION
Drugs that reduce postprandial blood glucose levels by inhibiting the rate of digestion of polysaccharides in the small intestine

4.4.1B MECHANISM OF ACTION
Acarbose and Miglitol inhibit the alpha-glucosidase enzyme that lines the brush border of the small intestine and is responsible for the hydrolysis of carbohydrates thereby delaying the absorption of glucose and other monosaccharides.

4.4.1C INDICATIONS AND CLINICAL USE
a) The control of postprandial hyperglycemia- should be taken with each meal
b) Acarbose and Miglitol do NOT cause HYPOGLYCEMIA
c) Acarbose and Miglitol are less potent than sulfonylureas or metformin – they decrease Hb1Ac by 0.5-0.8% points
d) Because different mechanism of action Acarbose and Miglitol have an additive effect on reducing glycemia together with either a sulfonylurea, metformin or insulin
e) Acarbose and Miglitol are not considered to be first line anti-diabetic drugs because of their reduced efficacy and poor tolerance due to side effects (see below)

4.4.1D ADVERSE EFFECTS
a) Unabsorbed carbohydrate causes abdominal pain, diarrheas and flatulence due to osmotic effect and bacterial fermentation
b) Many patients (25-45%) stop taking the drugs due to side effects
c) Do not cause hypoglycemia by themselves, but can increase the risk when given with a sulfonylurea or insulin
d) In event of hypoglycemia patients should be treated with oral administration of glucose not sucrose due to inhibitory effects of drug on the breakdown of sucrose

4.4.1E CONTRAINDICATIONS
a) Chronic intestinal disease
b) Inflammatory bowel disease
c) Colonic ulceration or any degree of intestinal obstruction

4.5 ORAL ANTI-DIABETIC DRUGS: SODIUM GLUCOSE LINKED TRANSPORTER 2 PROTEIN INHIBITORS
4.5.1 SGLT2 INHIBITORS
Canagliflozin (Invokana®) & Dapagliflozin (Farxiga®)

4.5.1A DESCRIPTION
Drugs that reduce hyperglycemia by promoting glucose excretion in the urine

4.5.1B MECHANISM OF ACTION
a) Inhibition of Sodium-Glucose Linked Transporter 2 protein (SGLT2) activity in the S1 segment of the proximal renal tubule prevents the normal process of glucose reabsorption leading to excretion of glucose in the urine

4.5.1C INDICATIONS AND CLINICAL USE
a) Improving glycemic control in Type 2 Diabetes- monotherapy or in combination
b) Decreases HbA1c by 0.5-0.9% low risk hypoglycemia when used as monotherapy
b) Body weight- ~ 80g of glucose (200-300 kCal) eliminated each day
d) BP- H2O eliminated by increased osmotic diuresis

4.5.1D ADVERSE EFFECTS
a) Urinary Tract Infections- genital mycotic infections
b) Thirst/Dehydration
c) Hypotension
d) LDL-Cholesterol
e) Hypoglycemia when given with other anti-hyperglycemia medications
f) Hyperkalemia- especially patients taking Meds that interfere with K+ excretion (e.g. K+ sparing diuretics)

4.5.1E CONTRAINDICATIONS
a) Renal impairment

4.6 ORAL ANTI-DIABETIC DRUGS: BROMOCRIPTINE
4.6.1 Bromocriptine (Cycloset)

4.6.1A DESCRIPTION
a) Sympatholytic Dopamine D2 receptor agonist
b) Quick Release formulation- taken within 2 hrs of waking
c) decreases HbA1c by ~ 0.5%
d) Dosage much lower than that used in Parkinson’s

4.6.1B MECHANISM OF ACTION
a) Exact MOA in diabetes is unknown
b) thought to act on the CNS to normalize the decreased AM dopamine levels present in Type 2 patients
c) Increased morning dopamine signaling antagonizes hypothalamic sympathetic nervous system leading to a decrease in hepatic gluconeogenesis, reduced lipolysis and lipogenesis, which in turn results in an increase in insulin sensitivity and glucose tolerance.

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<tr>
<th>DIABETES</th>
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<tr>
<td>↓Early morning Hypothalamic Dopamine levels</td>
<td>↑Hypothalamic Dopamine levels</td>
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<tr>
<td>↑Hypothalamic SNS</td>
<td>↓Hypothalamic SNS</td>
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<tr>
<td>↑Hepatic gluconeogenesis</td>
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<td>↑Lipogenesis/TG</td>
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• Glucose intolerance
• Insulin resistance
• Dyslipidemia
• ↑CVD

• ↑Glucose tolerance
• ↑Insulin sensitivity
• ↓Serum FFA
• ↓Vascular pathology

4.7 ORAL ANTI-DIABETIC DRUGS: COVELESELAM (Bile Acid-Binding resin)
4.7.1 Coveleselam
4.7.1A DESCRIPTION:
   a) A lipid-lowering drug used in the treatment of hypercholesterolemia
   b) Serendipitously found to have beneficial effects in diabetes
   c) Used as an **Adjunct “Add On”** anti-diabetic therapy to reduce blood glucose levels by indirectly increasing expression of GLP-1

4.7.1B MECHANISM OF ACTION
   a) Colesevelam binds bile acids in the small intestine forming insoluble complexes that are excreted in the feces
   b) Prevents reabsorption of bile acids
   c) Induces increased bile acid synthesis
   d) Bile acids bind to the TGR5 GPCR expressed on intestinal cells to stimulate GLP-1 secretion

4.7.1C INDICATIONS AND CLINICAL USE
   a) Add on therapy to metformin, sulfonylureas or insulin
   b) Decreases HbA1c by ~ 0.5%
   c) NOT considered **FIRST LINE** anti-diabetic drugs
   d) Useful in patients that also exhibit elevated LDL-cholesterol levels

4.8 INSULIN THERAPY THE TREATMENT OF TYPE 2 DIABETES
   a) As type 2 diabetes progresses beta cell function gradually declines and insulin therapy is often required to achieve satisfactory glycemic control. Insulin is the most effective medication at lowering glycemia.

   b) Insulin can be considered a first-line therapy for all patients with type-2 diabetes and should be the initial therapy for patients HbA1c>10%, fasting plasma glucose >250 mg/dL and random glucose consistently >300 mg/dL, Insulin is also the preferred 2nd line agent in patients with HbA1c > 8.5%.

   c) Insulin is indicated in patients presenting with a sudden onset of diabetes, significant recent weight loss, and polyuria accompanied by polydipsia- some of these patients may have late onset type 1 diabetes.

   d) Initial therapy is aimed at providing basal insulin with either intermediate (NPH) or long-term insulin (glargine) given once/twice daily before breakfast/dinner. The primary goal of basal insulin is to lower fasting glucose by inhibiting hepatic gluconeogenesis. Note that because of increased obesity and insulin resistance in type 2 diabetics considerably more insulin is required to treat these patients compared to those with type 1 diabetes.

   e) If necessary, insulin therapy can be intensified by the addition of regular- or rapid-acting insulin before selected meals in order to reduce postprandial glucose elevations. In this case, any insulin secretagogue medications should be eliminated.

   f) Disadvantages of insulin therapy: hypoglycemia, weight gain, and injection site lipodystrophy.

4.9 AMYLIN HOMOLOGS
Pramlintide (Symlin®)
4.9A DESCRIPTION
- Pramlintide is a synthetic analog of human Amylin, an endogenous neuroendocrine hormone that is synthesized by pancreatic beta cells and co-secreted with insulin, which contributes to glucose control in the postprandial period.
- Amylin production is absent in patients with diabetes.

4.9B MECHANISM OF ACTION
- Decreases hepatic gluconeogenesis.
- Decreases postprandial glucagon levels – i.e. resulting in a decrease in gluconeogenesis, glycogenolysis, and lipolysis.
- Slow gastric emptying - this slows the rate of delivery of glucose to the circulation thereby helping prevent excessive increases in the postprandial glucose concentration.
- N.B. gastric emptying is often increased in type 1 and type 2 diabetic patients and contributes to rapid rises in postprandial glucose seen in these patients.
- Increases satiety – i.e. reduces food intake.

Mechanism of Action:
- Pramlintide decreases hepatic gluconeogenesis, slows gastric emptying, decreases postprandial glucagon levels, and increases satiety.
- Because of short duration of action (2-3 hrs) primarily acts to decrease postprandial glucose elevations.

4.9 INDICATIONS AND CLINICAL USE
- Pramlintide is indicated as an ADJUNCT therapy in patients with either TYPE 1 or TYPE 2 diabetes who are using mealtime insulin therapy and who have not achieved adequate glycemic control.
- The effects of pramlintide are additive to insulin.
- Provides postprandial control of glucose levels and limits glucose fluctuations.
- Pramlintide needs to be injected subcutaneously before each meal.
- Pramlintide therapy decreases Hb1Ac by 0.5-0.7% points.
- Decreases amount of short acting insulin required.
- Can promote WEIGHT LOSS ~1-1.5kg over 6 months (may be due to GI side effects).
- Most appropriate for highly motivated patients who can tolerate nausea and are willing to add 2-4 more injections per day and more frequent glucose monitoring.
- Most likely to have greatest benefit in type 1 patients who are obese.

4.9D ADVERSE EFFECTS
- Nausea, vomiting, anorexia, headache.
- Together with insulin it increases the risk of severe hypoglycemia- the dose of insulin should be reduced ~50%.
4.9E DRUG INTERACTIONS
Due to the slowing of gastric emptying it can affect the absorption of other orally administered
drugs (e.g. contraceptives & antibiotics), which should be taken 1 hr before or 2 hrs after

5. CURRENT RECOMMENDATIONS OF THE ADA/EASD FOR THE MANAGEMENT
OF TYPE 2 DIABETES
a) Patients should initially undergo life style changes including diet and exercise to improve
glycemia, blood pressure and lipid profile.
b) However, continuous treatment with oral anti-diabetic medications will typically be
required to maintain normal or near normal glycemia.
c) Metformin therapy should be the first drug of choice in most patients. The Metformin
dose should be titrated over a two-month period to the maximally effective dose
(typically 850 mg twice a day). Advantages: Efficacy, Safety, Weight Loss, no risk of
hypoglycemia and beneficial effects on CVD mortality.
d) In cases where metformin is specifically contraindicated (e.g. elderly patients, renal
hepatic, or cardiac disease, excess alcohol) another oral agent should be used (i.e. a
sulfonylurea or thiazolidinedione).
e) If after 2-3 months adequate glycemic control is NOT achieved (i.e. HbA1c remains
>7%), another medication should be added e.g. a sulfonylurea (least expensive),
thiazolidinedione (no hypoglycemia), exenatide (maybe useful in overweight patients), or
insulin (most effective; especially if HbA1c is > 8.5%).
f) Further adjustments to therapy should be made no less frequently than every three
months.
g) In those patients that fail to achieve adequate control of glycemia on a combination of
two drugs a third drug or insulin can be added, or the insulin therapy regimen can be
intensified.
### SUMMARY: INSULIN PREPARATIONS

#### Properties of commercially-available Insulin Preparations

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<thead>
<tr>
<th>Formulation</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>5-15 mins</td>
<td>45-75 mins</td>
<td>2-4 hrs</td>
<td>For meals or acute Hyperglycemia; Can be injected immediately before meals</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td></td>
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<tr>
<td>Insulin glulisine</td>
<td></td>
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</tr>
<tr>
<td><strong>Regular Insulin</strong></td>
<td>30-60 mins</td>
<td>2-4 hrs</td>
<td>6-8 hrs</td>
<td>For meals or acute Hyperglycemia; Needs to be injected 30-45 mins prior to meal</td>
</tr>
<tr>
<td>NPH Insulin (Isophane)</td>
<td>1.5-2 hrs</td>
<td>6-10 hrs</td>
<td>16-24 hrs</td>
<td>Provides basal insulin and overnight coverage</td>
</tr>
<tr>
<td><strong>Intermediate acting</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insulin glargine</td>
<td>~2 hrs</td>
<td>No Peak</td>
<td>20-&gt;24 hrs</td>
<td>Provides basal insulin and overnight coverage</td>
</tr>
<tr>
<td>Insulin detmir</td>
<td></td>
<td>No Peak</td>
<td>6-24 hrs</td>
<td></td>
</tr>
</tbody>
</table>
### SUMMARY DRUGS TO TREAT TYPE 2 DIABETES

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-IV Inhibitors</td>
<td>Sluggens/Saxagliptin</td>
<td>0.48-0.6% - 24 hrs</td>
<td>Decreases blood glucose, improves glycemic control</td>
<td>Nausea, skin rash, hypoglycemia</td>
<td>Liver disease, renal impairment</td>
</tr>
<tr>
<td>Incretin Mimetics</td>
<td>Exenatide, Liraglutide</td>
<td>0.5-1.0%</td>
<td>Improves glycemic control for up to 3 years</td>
<td>Weight loss, nausea, vomiting</td>
<td>GI tract abnormalities</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td>Acarbose, Miglitol</td>
<td>0.5-1.0%</td>
<td>Slows carbohydrate absorption in the small intestine</td>
<td>Flatulence, diarrhea</td>
<td>Liver disease, renal impairment</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>0.5-1.4%</td>
<td>Improves insulin sensitivity and glycemic control</td>
<td>Weight gain, fluid retention, bone fractures</td>
<td>Liver disease, renal impairment</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide, Nateglinide</td>
<td>1.15%</td>
<td>Increases glucose utilization in type 2 diabetes</td>
<td>Hypoglycemia, headache</td>
<td>Liver disease, renal impairment</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Chlorpropamide, Tolbutamide</td>
<td>-1.5%</td>
<td>Improves glycemic control within 24 hours</td>
<td>Weight gain, hypoglycemia</td>
<td>Liver disease, renal impairment</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td>-1.5%</td>
<td>Improves insulin sensitivity and glycemic control</td>
<td>Weight loss, diarrhea</td>
<td>Liver disease, renal impairment</td>
</tr>
</tbody>
</table>

**HbA1c Decrease Effect**
- To/Chi: Lowers fasting glucose
- FGR: Fast-acting insulin
- KGR: Slow-acting insulin

**Adverse Effects**
- Lactic acidosis
- Cerebrovascular accident
- Seizure, hypoglycemic coma
- Hypoglycemia
- Hypersensitivity (Type 1 diabetes)

**Contraindications**
- Pregnancy
- Severe heart failure
- Hypersensitivity
- Liver disease, renal impairment
- Sulfa drug allergy

**Drug Interactions**
- Decreased metabolism
- Increased hypoglycemia
- Increased hypoglycemia
- Increased lactic acidosis
- Increased hypoglycemia
- Increased hypoglycemia
- Increased hypoglycemia

**Warnings**
- Liver disease, renal impairment
- Sulfa drug allergy
- Pregnancy
- Severe heart failure
- Hypersensitivity
<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Mechanism</th>
<th>HbA1c Decrease</th>
<th>Duration of Effect</th>
<th>Advantage</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramlintide</td>
<td>Amylin mimic Adjunct to insulin therapy ↓Postprandial glucose ↑Hepatic gluconeogenesis Slows gastric emptying ↑Satiety</td>
<td>0.5-0.7%</td>
<td>2-3 hrs</td>
<td>↓Postprandial glucose Weight loss</td>
<td>Requires injections Nausea Hypoglycemia (especially with insulin need to reduce insulin by 50%)</td>
<td></td>
</tr>
<tr>
<td>SGLT2 inhibitors Canagliflozin dapagliflozin</td>
<td>Inhibits glucose renal reabsorption by inhibiting SGLT2 promotes increased glucose excretion in urine</td>
<td>0.5-0.9%</td>
<td>&gt;24 hrs</td>
<td>↓Blood pressure Weight loss</td>
<td>Urinary tract infections Thirst/Dehydration Hypotension ↑LDL Cholesterol Renal impairment Type 1 diabetes</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine (Cycloset)</td>
<td>Dopamine D2 agonist acts on the CNS to normalize hypothalamic dopamine levels thereby decreasing Sympathetic tone resulting in: ↓Hepatic gluconeogenesis ↓Lipolysis/FFA ↑Lipogenesis/TG ↑Glucose tolerance ↑Insulin sensitivity</td>
<td>~0.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid-binding resin Covelesalam</td>
<td>Prevent bile acid reabsorption Promoting increased bile acid synthesis Bile acids bind TGR5 GPCR on intestinal cells to induce GLP-1 secretion</td>
<td>~0.5%</td>
<td></td>
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</tbody>
</table>
Adrenocorticosteroid Hormones and Adrenocorticoid synthesis inhibitors

Date: Monday March 30th, 2015, 8:30am -10:00am


Key Concepts and Learning Objectives

1. Describe the principal physiological responses to both glucocorticoids and mineralocorticoids.

2. Describe the role of the Hypothalamus-Pituitary-Adrenal (HPA) axis in the regulation of aldosterone, cortisol and androgen synthesis and the mechanisms by which cortisol and exogenous glucocorticoids act to negatively regulate the HPA axis.

3. Describe the differences between the differential temporal synthesis of endogenous cortisol and aldosterone that occurs throughout the day.

4. Describe the mechanism of action of glucocorticoids and mineralocorticoids, including the mechanisms by which glucocorticoids act to inhibit the immune system.

5. Discuss the structure/function relationships of endogenous and synthetic glucocorticoids, and the role of 11-beta hydroxysteroid dehydrogenase enzymes in the regulation of cortisol activity.

6. Discuss the role of corticosteroid structure and the 11-beta hydroxysteroid dehydrogenase enzymes in influencing the clinical effectiveness of synthetic glucocorticoids administered via different routes.


8. Describe the indications and clinical uses of synthetic glucocorticoid drugs in the treatment of non-endocrine diseases such as rheumatoid arthritis, asthma, inflammation, respiratory distress syndrome, cancer and cerebral edema.

9. List the major adverse effects associated with the clinical use of chronic glucocorticoid therapy.

10. Describe the consequences of abrupt withdrawal of chronic glucocorticoid therapy and the underlying mechanisms involved.

11. Describe the use of dexamethasone in the diagnosis of Cushing’s Disease.

12. List the drugs used in the medical treatment of Cushing’s disease and describe the mechanisms involved.
Drugs to be covered in this lecture:

**Principal synthetic corticosteroids**
Hydrocortisone (Cortisol)
Cortisone
Fludrocortisone
Prednisone
Prednisolone
Dexamethasone

Inhaled forms of glucocorticoids used in asthma:
Triamcinolone acetonide, beclometasone & fluticasone

Drugs used to treat Cushing’s Disease

**Adrenocorticoid synthesis inhibitors**
Ketoconazole
Metyrapone
Etomidate

**Adrenocorticolytic Drugs**
Mitotane

**Glucocorticoid Receptor Antagonists**
Mifepristone
ADRENOCORTICOID HORMONES

1. Hormones of the Adrenal Cortex: An overview
(A) The adrenal cortex synthesizes two major classes of steroid hormones:

Corticosteroids
(i) Glucocorticoids - the principal glucocorticoid is CORTISOL
- regulation of intermediary metabolism
- regulation of the immune system

(ii) Mineralocorticoids – the principal mineralocorticoid is ALDOSTERONE
- regulation of electrolyte and fluid balance

Corticosteroids are essential for life and play a critical role in the physiological response to stress and changes in the environment

Androgens
- female sexual development (major source of testosterone)
- Conditions leading to increased androgen levels in females can lead to increased virilization of the genitalia
- Little significance in males

The focus of this lecture is on the physiology and pharmacology of the corticosteroids

(B) Regulation of corticosteroid synthesis
(i) Adrenal steroid hormones are synthesized from cholesterol in distinct regions of the Adrenal Cortex

Zona glomerulosa- outermost zone of the cortex
- Synthesizes ALDOSTERONE
- Regulated by the Renin-angiotensin system and by the serum concentrations of potassium ions. ACTH is permissive for aldosterone synthesis

Zona fasciculata- middle zone of the cortex
- Produces glucocorticoids, principally CORTISOL
- Regulated by pituitary production of ACTH

Zona reticularis- inner zone of the cortex next to the adrenal medulla
- Responsible for androgen production
- Regulated by ACTH

(ii) The synthesis of adrenal steroid hormones by the adrenal cortex is regulated by the Hypothalamic -Pituitary-Adrenal (HPA) axis.

(iii) Corticotropin-releasing hormone (CRH) is released by the hypothalamus in response to circadian rhythms and a number of stress inducers such as acute trauma, surgery, fever, infection and pain.

(iv) CRH acts via its GPCR expressed on the cells of the corticotropes of the Anterior Pituitary to induce the synthesis and release of adrenocorticotropic hormone (ACTH).
(v) ACTH binds to its coupled receptor on the adrenal cortex and induces the expression of genes involved in the synthesis of all adrenal steroid hormones.

(vi) Importantly, Cortisol produced by the adrenal cortex acts in a negative feedback loop to inhibit the HPA axis by inhibiting the production of both CRH and ACTH.

2. Physiological effects of glucocorticoids

2.1. Carbohydrate and Protein metabolism:
Liver
- ↑gluconeogenesis and ↑glycogen storage

Periphery
- ↑Protein catabolism (muscle) = ↑substrate for gluconeogenesis
- ↓Peripheral glucose utilization
- ↑Blood glucose

2.2. Lipid Metabolism:
- ↑Lipolysis by facilitating action of GH/β-adrenergic agents
- ↑glycerol = ↑substrate for liver gluconeogenesis
- ↑FFA contributes to ↑Insulin resistance
- Redistribution of Fat:
  - ↑Truncal obesity
  - ↑Back of neck (Buffalo hump)/Upper Chest
  - ↑Facial plethora/Moon Facies
  - ↓Extremities

2.3. Response to Stress
- Cortisol levels increase in times of stress
- the corresponding increase in blood glucose acts to protect glucose-dependent tissues (e.g. brain/kidney/heart) from starvation

2.4. Cardiovascular system
- modulate vascular reactivity to vasoactive agents e.g. norepinephrine and vasopressin
- Adrenal insufficiency results in HYPOTENSION
- Excess glucocorticoids (i.e. Cushing’s Disease) results in HYPERTENSION

2.5. Inhibition of the immune system:
- ↓numbers of circulating T cells, B cells, macrophages, eosinophils & basophils- redistribution to lymphoid tissues
- inhibition of cytokine synthesis
- inhibition of PLA2 activity- by upregulation of Annexins
- inhibition of COX-2 synthesis- ↓prostaglandin production
- serves to limit the extent of the immune and inflammatory responses
2.6. Skeletal muscle
- permissive concentrations of glucocorticoids required for muscle function
- muscle weakness is a sign of adrenocortical deficiency (Addison’s Disease)

2.7. Other Systems
GI tract - glucocorticoids promote synthesis of gastric acid & pepsin
- ↓GI absorption of Ca²⁺

Bone - glucocorticoids promote bone loss: ↓osteoblasts & ↑osteoclasts

CNS - affect mood behavior and brain excitability
glucocorticoid excess (e.g. Cushing’s Disease)- mood elevation
glucocorticoid deficiency (Addison’s Disease)- apathy/depression

2.8. ***Feedback inhibition of the Hypothalamic-Pituitary-Adrenal Axis***
- Homeostatic mechanism to prevent excessive glucocorticoid synthesis
- Cortisol/glucocorticoids act to inhibit synthesis of both CRH & ACTH
- Inhibition of ACTH production blocks Adrenal synthesis of cortisol
- In cases of chronic exogenous glucocorticoid drug treatment the production of ACTH is directly suppressed.
- As ACTH is a trophic factor for the Zona fasiculata/Zona reticularis, this results in the atrophy of these regions, thereby resulting in the loss of endogenous Cortisol production (Aldosterone production left largely intact).
- This loss of endogenous cortisol production results in adrenal insufficiency (a life-threatening condition).
- Recovery of normal adrenal function can take many months (up to 12 months)

3. Physiological effects of Mineralocorticoids
a) Aldosterone is the primary mineralocorticoid

b) Controls body fluid volume and electrolyte balance

c) Aldosterone acts on the kidney tubules and collecting ducts to promote:
   ↑ expression of the Na+/K+ ATPase
   ↑ reabsorption of Na+ and H2O
   ↑ excretion of K+ and H+

   **Aldosterone excess**
   - ↑ Na+ reabsorption
   - ↑ extracellular fluid volume
   - ↑ Alkalosis
   - Hypertension
4. Corticosteroids: Synthesis and Metabolism

a) Both cortisol and aldosterone are synthesized from cholesterol.

b) Normal adults secrete: 10-20 mg of cortisol daily
0.125 mg of aldosterone daily

c) The rate of secretion of cortisol is controlled by a circadian rhythm that peaks at ~8AM
Cortisol plasma concentration: ~16 mcg/dL at 8AM
~4 mcg/dL at 4PM

Aldosterone plasma concentrations are constant at ~0.01 mcg/dL

d) Cortisol levels are also significantly increased (4-6 fold) in response to stress.
- this is caused by stress inducing the hypothalamus to increase production of CRH, which in turn leads to increased production of ACTH that acts directly on the adrenal cortex to induce cortisol production.

e) ~95% of cortisol is bound to plasma proteins
CBG - Corticosteroid Binding Globulin (high affinity/low capacity)
- only unbound cortisol is bioavailable
- binding is saturated when cortisol concn > 20-30 mcg/dL
- most synthetic corticosteroids do not bind CBG

Aldosterone does not bind to plasma proteins

f) Cortisol, aldosterone and all synthetic corticosteroids are metabolized by the LIVER, where they are reduced and conjugated to glucuronic acid making them more water soluble and thereby greatly enabling RENAL excretion in the urine.

Serum half lives: Cortisol 60-90 mins
- Aldosterone 15-20 mins

g) The half-life of corticosteroids can be elevated in patients with HEPATIC dysfunction.

5. Corticosteroids: Mechanism of Action

a) Cortisol and other glucocorticoids are steroids that readily cross the plasma membrane and mediate their effects through specific glucocorticoid receptors (GR) that act as transcription factors.
b) In unexposed cells GR exist in the cytoplasm in a complex with a number of proteins including Heat shock-90 and immunophilin-56 proteins.

c) The binding of cortisol to GR promotes (i) a conformational change, (ii) dissociation from Hsp90 and IP56, (iii) dimerization and (iv) translocation into the nucleus.

d) Once in the nucleus, GR binds to specific promoters via its cognate target sequence the glucocorticoid-response element (GRE), where it recruits additional transcriptional cofactors and acts to either promote or inhibit gene expression.

e) **Aldosterone works in a similar fashion via the mineralocorticoid receptor (MR)**

### 6. The role of 11β-hydroxysteroid dehydrogenase in corticosteroid specificity

a) Cortisol is not a “pure” glucocorticoid- it also exhibits some mineralocorticoid activity.
   - In fact, cortisol binds with equal affinity to both the GR and the MR.

b) Furthermore, cortisol is found at much higher concentrations in plasma (16 mcg/dL cortisol versus aldosterone).

C) The specificity of corticosteroid action is maintained by the hydroxysteroid dehydrogenase (11β-HSD).

### d) The 11β-HSD enzyme isoform is expressed in key aldosterone-sensitive tissues (kidney, salivary gland & colon) and converts cortisol to the inactive metabolite cortisone (which doesn’t bind to either GR or MR).

- This prevents higher serum levels of cortisol from inappropriately activating the MR in the kidney & colon to induce an aldosterone-like response.

e) The liver expresses the 11β-HSD enzyme isoform that converts cortisone back into active cortisol.

### 7. Structure function of synthetic Corticosteroids

A large number of synthetic corticosteroids have been synthesized and are used in clinical practice. These synthetic drugs differ based upon their respective levels of glucocorticoid and mineralocorticoid activity, as well as their topical potency and duration of biological activity.
8. Effects of Structure Function on Routes of Administration

a). Oral administration
   - can use both active and inactive agents
   - inactive agents will be converted to active agents in liver (11b-HSD1)

b). Topical application to skin to treat inflammation/insect bites
   - 11beta-HSD1 not expressed in the skin
     i.e. cortisone/prednisone will be inactive
   - must use active ingredient i.e. hydrocortisone/prednisolone

c). Direct injections into the joint for treatment of RA
   - 11beta-HSD1 not expressed in the joint
   - must use active agent e.g. prednisolone NOT prednisone

d). In utero treatment of fetus
   - placenta expresses 11 beta-HSD2 (inactivates maternal hormone)
   - fetal liver not active, so unable to activate inactive agents
   - therefore use dexamethasone-treatment of mother which can cross the placenta without inactivation (not a substrate for 11bHSD2) and acts directly on target tissues in the fetus

8. Corticosteroids: Clinical Uses

Hormone replacement therapy - PHYSIOLOGICAL DOSES
   - hydrocortisone/fludrocortisone
   - Acute adrenal insufficiency
   - Chronic adrenal insufficiency
     - Congenital adrenal hyperplasia

Non-endocrine therapy - PHARMACOLOGICAL DOSES
   - prednisone/dexamethasone etc
   - Rheumatoid Arthritis
   - anti-inflammation
   - asthma
   - cancer
   - respiratory distress syndrome
   - cerebral edema

9. Adrenal Insufficiency
i) Inability of the Adrenal cortex to produce adequate amounts of hormones
ii) Potentially life threatening disorder, although some patients do not exhibit symptoms
unless severely stressed

**A. Primary Adrenal Insufficiency (Addison’s Disease):**
- Autoimmune destruction of the adrenal cortex (70%)
- Tuberculosis (20%)
- Other e.g. fungal infection/hemorrhage/cancer (10%)
  - Affects both cortisol and aldosterone production

**B. Secondary Adrenal Insufficiency:**
- Defects in either ACTH or CRH production (10%)
- Iatrogenic suppression of HPA axis with exogenous glucocorticoids (90%)
  - Primarily affects only cortisol production (zona glomerlusa intact)

**Treatment Goal:** To replace the physiological activity of the “missing hormones”

**Cortisol Replacement Therapy:**
- **Hydrocortisone** (20-30 mg/day) given 2-3 times/day in divided doses
  - alternatively, longer acting glucocorticoids such as either **Prednisone** (5 mg/day) or **Dexamethasone** (0.5 mg/day) can be given once daily, typically before bedtime (smoother effect)
- although hydrocortisone has some mineralocorticoid activity this is not sufficient to replace aldosterone, while both prednisone and dexamethasone completely lack any salt-retaining activity

_Aldosterone Replacement Therapy:_
- aldosterone itself is not used for replacement therapy due to high cost and rapid hepatic metabolism to inactive metabolites

- drug of choice is **Fludrocortisone** (0.1 mg/day) a potent synthetic mineralocorticoid

- although Fludrocortisone also has some glucocorticoid activity it does not exhibit anti-inflammatory activity at the doses given

C. Treatment Regimens

**Primary Adrenal Insufficiency**
- Hydrocortisone (or Dexamethasone)- CORTISOL REPLACEMENT
- Fludrocortisone - ALDOSTERONE REPLACEMENT

**Secondary Adrenal Insufficiency**
- Hydrocortisone (or equivalent dose of Dexamethasone)
- Mineralocorticoid therapy is **not usually necessary** as the zona glomerulas remains intact

**Acute Adrenal Insufficiency/Acute Adrenal Crisis**
- may occur:  
  a) in an undiagnosed patient after serious illness
  b) in a patient that does not increase dose of glucocorticoid during acute infection
  c) after abrupt withdrawal of chronic glucocorticoid therapy

- typically presents as hypovolemic circulatory shock plus nausea, vomiting, weakness, fatigue, fever, hyponatremia and hyperkalemia

- initial treatment is **ELECTROLYTE REPLACEMENT** 0.9% saline followed by **IV hydrocortisone** (or Dexamethasone)

- mineralcorticoid therapy is **not useful initially** as it takes days for effect

- once patient is stable, IV hydrocortisone is tapered over 1-3 days to an oral maintenace dose of hydrocortisone plus fludrocortisone

**10. Assesment of treatment efficacy and dosage adjustments**

a) Lowest dose that relieves the symptoms of glucocorticoid deficiency and decreases hyperpigmentation (only present in primary disease due to increased MSH as a result of ACTH overproduction)

b) Evidence of ↑weight gain, facial plethora and other “Cushingoid symptoms” is indicative of excessive dosing

c) In normal individuals Cortisol levels are naturally increased in response to stress.
Therefore dosage adjustments are made under the following conditions:

(i) Minor illness  
(ii) Surgery  
(iii) Pregnancy  

11. Congenital Adrenal Hyperplasia  

a) A group of genetic disorders that cause a deficiency in the activity of certain enzymes (i.e. steroid 21-hydroxylase) involved in the synthesis of Glucocorticoids  

b) Impaired production of cortisol results in a lack of negative feedback and increased expression of ACTH, resulting in excess production of other hormonally active steroid hormones e.g. **ANDROGENS**

c) Newborns are born with ambiguous genitalia

d) Affected males are normal at birth, but may develop precocious secondary sexual characteristics

e) In a subset of patients mutations in CYP21 can severely inhibit enzyme activity resulting in a deficiency in aldosterone synthesis - as a result these patients are unable to retain Na+ and are referred to as “Salt Wasters”. If untreated these newborns will typically develop an acute adrenal crisis within 2-3 weeks of birth

f) Treatment: **Hydrocortisone** AND (if necessary) **Fludrocortisone**

g) Treatment Goal: Restore hormones to the normal range to avoid adrenal crisis and to suppress ACTH production thereby abrogating ANDROGEN overproduction

- Sudden growth spurts indicate inadequate treatment
- Growth failure suggests excessive glucocorticoid treatment

h) Prenatal screening of amniotic fluid for 17-hydroxyprogrenolone identifies affected individuals. These patients can be treated **in utero** by administration of dexamethasone to the mother. Prior to the 9th week of gestation this effectively suppresses the excess production of androgens and prevents female virilization and related problems. If subsequent karyotype analysis from chorionic villus sampling at approximately 16 weeks reveals a male child, treatment can be delayed until birth.
12. Non-Endocrine Uses of Glucocorticoids

12.1. Rheumatoid Disorders: e.g. RA, SLE, vasculitis
   a) Prednisone is typically the drug of choice- **Acts by inhibiting the ongoing active autoimmune response**
   b) used for short periods (usually < 3-4 weeks) to provide **symptomatic pain relief** and to control disease “flare ups”
      N.B. treatment does not **cure** the underlying disease etiology
   c) used as a therapeutic bridge while waiting for effects of long acting DMARDs
   d) more effective than NSAIDs when used for < 1 month
      - ↓ Joint tenderness, ↓ pain & ↑ grip strength
   f) short-term low-dose (<15 mg/day) is seldom associated with adverse effects
   g) drugs can be administered directly into joint (max. once every 3 months)
      - active form of drug e.g. Prednisolone must be used
   h) In more severe cases low dose **chronic** treatment has also been shown to reduce bone erosions- however decreased efficacy after 6 months and increased potential for adverse effects especially **OSTEOPOROSIS**
      - patients should take daily Ca^{2+} and Vitamin D supplementation
   i) Once there is clinical improvement, the dose of glucocorticoid should be slowly tapered to avoid serious adverse effects

12.2. Treatment of Allergies
   a) e.g. bronchial asthma, allergic rhinitis, drug/serum/transfusion-related allergic diseases, contact dermatitis, urticaria, bee stings and insect bites
   b) Treatment is **not curative** - only treats symptoms
   c) Acts to inhibit the inflammatory response and cytokine production
   d) for respiratory-system allergies drugs can be administered in inhaled form e.g. triamcinolone and/or beclomethasone
      - Allows delivery of high concentrations of drug directly to the lung
      - Due to significant 1st pass effect only < 1% of any swallowed glucocorticoid is bioavailable, limiting risk of adverse effects and reducing the risk of HPA suppression
      - If asthmatic patient is treated chronically with systemic oral glucocorticoids and is then **switched** to inhaled glucocorticoids
        - (i.e. a **much lower systemic dose**) - care must be taken to not abruptly stop the administration of the systemic drug, as this can precipitate an **ACUTE ADRENAL CRISIS**
   e) for serious acute cases of asthma short term oral glucocorticoids or IV administration can be used e.g. prednisolone
12.3. **Organ transplants**
- prevents graft rejection by inhibiting host immune system

12.4. **Kidney**
- glucocorticoids are used in treating the nephrotic syndrome caused by minimal change disease, which results from an inflammatory infiltrate into the kidney

12.5. **Treatment of a number inflammatory conditions**
- Skin: treatment of inflammatory dermatoses e.g. psoriasis
- Inflammatory eye diseases: e.g. allergic conjunctivitis
- GI tract e.g. inflammatory bowel disease and ulcerative colitis

12.6. **Cancer**
- treatment of acute lymphocytic leukemias and lymphomas
- reduces the numbers of lymphocytes/leukocytes in the blood

12.7. **Respiratory distress syndrome**
- respiratory distress is common in premature infants
- mothers treated with **dexamethasone** prior to birth
- **dexamethasone** is **not metabolized by** 11βHSD2 and freely crosses the placental barrier where it can **promote lung maturation**
- **prednisone** is **NOT USED** as prednisolone formed in the maternal liver is converted to prednisone by placental 11bHSD2, and since the fetal liver does not operate during fetal life it **cannot** be converted to the active **prednisolone** in the fetus

12.8 **Treatment of cerebral Edema**
Dexamethasone is used to decrease intracranial pressure due to vasogenic cerebral edema in the following conditions:
- Primary and metastatic brain tumors
- Bacterial meningitis (prevents hearing loss)
- Brain radiation exposure
- High altitude cerebral edema
Not to be used for traumatic brain injury, stroke or intracerebral hemorrhage

Mechanism of action though to involve:
- ↓inflammation and ↓cytokine production
- ↑Stabilization of blood brain barrier
- ↓Endothelial permeability
- ↓CSF production ↑reabsorption
- ↑CSF-mediated fluid clearance

13. **Effects of glucocorticoids on the immune system.**
Glucocorticoids can inhibit the immune response by several mechanisms:
- a) The NF-kB transcription factor is involved in the regulation of many genes involved in the regulation of the immune response including cytokines, cytokine receptors, chemokines, and COX-2. One of the target genes of glucocorticoids is
**IκB**, a specific inhibitor of NF-κB that binds to NF-κB causing it to dissociate from DNA and recycle back into the cytoplasm.

b) Glucocorticoids can also directly inhibit the activity of other transcription factors known to play a critical role in the regulation of the immune response e.g. AP-1

c) Glucocorticoids can also specifically directly repress the expression of other genes known to be critical for the regulation of the immune response

14. **Glucocorticoid: Adverse effects**

Glucocorticoids can cause adverse effects by two major mechanisms:

I. **Abrupt withdrawal of glucocorticoid drugs**
   a) **HPA suppression and acute adrenal insufficiency (serious)**
      - chronic glucocorticoid treatment (>20 mg prednisone for >3 weeks) can result in significant HPA suppression i.e. inhibition of ACTH/CRH

      - the inhibition of ACTH production (a trophic factor for the zona fasciculata/reticularis) results in **atrophy** of the adrenal cortex and a subsequent **deficiency** in endogenous cortisol production

      - **ABRUPT** withdrawal of chronic glucocorticoid therapy will uncover this cortisol production deficiency and can precipitate an **ACUTE ADRENAL CRISIS**

      To **avoid** adrenal crisis, chronic glucocorticoid therapy should be **slowly tapered** (~10-20% decrease in dose every 1-2 weeks)

   b) **“Flare up” of underlying disease (common)** e.g. Rheumatoid Arthritis
      - withdrawal of glucocorticoids allows the underlying overactive immune
system to re-establish the disease process
- this can be significantly exacerbated if there is any significant
  suppression of the HPA axis i.e. reduced endogenous cortisol

II. Exaggerated supraphysiological responses caused by pharmacological doses of glucocorticoids

↑Appetite- increased production of neuropetide Y promotes feeding behavior
↑Weight gain- especially truncal obesity/upper chest/neck
Facial plethora/Moon Facies - puffy face
Diabetes - hyperglycemia/insulin resistance
Edema-electrolyte & water imbalance caused by excess mineralocorticoid activity
Hypertension- due to enhancement of vasoactive agent response
↑Cardiovascular disease- MI and stroke
Muscle myopathy - specifically upper/lower extremities (common)
↑Osteoporosis- GI Ca²⁺ uptake; osteoclasts; osteoblasts
↑Osteonecrosis
↑Peptic Ulcers - increased production gastric acid/pepsin
↑Risk of infection - inhibition of immune system - e.g. pneumonia
Impaired wound healing- decreased expression of growth factors/matrix proteins
Emotional disturbances - euphoria/psychosis
Glaucoma/Cataracts - common, especially with eye drop use
Growth retardation in children
Cushing’s syndrome- caused by chronic excess of glucocorticoids in the blood and includes many of the above symptoms

15. Disease of glucocorticoid excess: Cushing’s Disease/Cushing’s Syndrome

Causes: An excess of glucocorticoid activity (either endogenous or exogenous)

Symptoms: truncal obesity, buffalo hump, moon facies, muscle weakness, hypertension, hyperglycemia/insulin resistance, thinning of the skin, easy bruising and female hirsuitism

Exogenous:
- most commonly caused by prolonged exogenous administration of glucocorticoids

Treatment: Slow tapering of exogenous glucocorticoids

Endogenous:
a) Cushing’s Disease (70%) - Pituitary adenoma hypersecreting ACTH resulting in increased cortisol production from the adrenal gland (incidence ~1-2 /100,000)

b) Ectopic ACTH syndrome (15%) e.g. ectopic production of ACTH by lung tumor

c) Primary adrenal cortisol-secreting tumor (15%)
16. Diagnosis of Cushing’s Syndrome

a) **Late Night Cortisol levels:** In normal individuals cortisol levels fluctuate based upon a circadian rhythm. Maximal levels occur around 8 AM (range 10-20 mcg/dL) and decline throughout the day reaching their minimum levels around midnight (~1.8-4 mcg/dL). Individuals with Cushing’s syndrome exhibit elevated cortisol levels at midnight. Hence, one way of identifying putative Cushing’s patients is by determining late night cortisol levels.

b) **Low dose dexamethasone suppression test:** In normal individuals cortisol levels are subject to negative feedback regulation. If a normal patient is administered 1 gm of dexamethasone at 11 pm it will act to inhibit the expression of ACTH resulting in a suppression of serum cortisol levels at 8 am (should be < 1.8 mcg/dL). Conversely, since someone with Cushing’s disease is producing excess levels of ACTH due to the presence of a Pituitary tumor, the low level of dexamethasone used in this assay will likely not be sufficient to significantly reduce the level of 8 am serum cortisol.

c) **High dose dexamethasone suppression test:** This test distinguishes between Cushing’s syndrome caused by an ACTH-producing pituitary tumor versus disease caused by a tumor ectopically secreting ACTH. In this test, individuals are monitored for 2 days to determine their basal levels of cortisol and are then administered 8 mg dexamethasone at 11pm. In normal individuals, their 8 am serum cortisol levels are typically close to 0 mcg/dL. In individuals with Cushing’s disease due to production of ACTH from a pituitary tumor, this high level of dexamethasone will be sufficient to partially suppress the tumor production of ACTH, resulting in an 8 AM cortisol level of ~5 mcg/dL. Conversely, if the ACTH is ectopically produced by a non-pituitary tumor, that tumor will not be subject to the negative influence of the dexamethasone and as a result 8AM cortisol levels will not be reduced.
17. Adrenocorticoid Synthesis Inhibitors used in the treatment of Cushing’s Syndrome

The first line treatment for Cushing’s Disease or Cushing’s syndrome is removal of the tumor and or irradiation of the tumor. However, in cases where tumor surgery is either not possible or is refused, the disease can be treated medically with drugs that inhibit cortisol synthesis.

**Goal:** To reduce elevated cortisol levels back to the normal range by inhibiting enzymes involved in cortisol biosynthesis

**A. Ketoconazole:**

a) An anti-fungal agent typically used to inhibit fungal P450 enzymes

b) When used at higher concentrations it inhibits:

- **CYP11B1** - the final enzyme in cortisol biosynthesis
- **CYP11A1** - the enzyme involved in the conversion of cholesterol to pregnenolone - the first and rate-limiting step in the biosynthesis of all adrenal steroids

c) Also inhibits ACTH secretion by an unknown mechanism

d) Should not be used in pregnancy

**B. Etomidate:**

a) An IV anesthetic that inhibits both CYP11A1 and CYP11B1

**C. Metyrapone:**

a) Inhibits 11β-hydroxylase (CYP11B1) - the enzyme involved in the final step of cortisol biosynthesis. It also inhibits aldosterone synthase (CYP11B2), the last step in aldosterone production.

Note: The effects on electrolyte balance caused by decreased aldosterone production are mitigated by an increase in 11-deoxycorticosterone, which possess some mineralocorticoid activity.
b) Can cause female hirsutism due to the build up of androgen precursors

c) Only adrenocortical inhibitor that is safe for use during pregnancy

**Note:** Individually these drugs diminish the high level of endogenous cortisol production caused by the tumor, but typically are unable to completely reduce cortisol to normal levels.

**Combination therapy:** Drugs act synergistically to inhibit cortisol biosynthesis, consequently a combination of drugs gives greater therapeutic benefit than monotherapy and reduces the risk of side effects.

**Risks**
All of these drugs inhibit endogenous corticosteroid production and therefore can potentially precipitate adrenal insufficiency. Drugs must therefore be used at the appropriate dose and the activity of the HPA axis must be closely monitored.

**D. Mitotane (Active ingredient of the DTT insecticide)**

a) Adrenocortiolytic drug used to achieve medical adrenalectomy in cases of severe Cushing’s Disease where patients are not cured by surgery or refuse surgery

b) Metabolized in the adrenal gland by CYP11B1 and CYP11A1 to a compound that induces mitochondrial destruction and necrosis of adrenocortical cells, thereby acting to prevent cortisol production

c) Goal of therapy is to completely ablate endogenous cortisol production

d) As serum cortisol levels fall patients will require glucocorticoid supplementation with either hydroxycortisone, prednisone or dexamethasone

e) Mitotane typically spares the zona glomerulosa, so mineralocorticoids are not usually required

f) Contraindicated in Pregnancy- due to permanent fatal adrenal damage

g) Side Effects: nausea, vomiting, anorexia, rash, diarrhea, ataxia, hypercholesterolemia and hepatotoxicity - not well tolerated ~80% of patients require dose reduction

**E. Mifepristone**
- Progesterone Receptor antagonist
- antagonizes Glucocorticoid receptors at high doses
- prevents excessive activation of GR in Cushing’s Disease
- approved for treatment of refractory Cushing's

**Adverse Effects**

Can cause Adrenal Insufficiency (needs to be monitored)
Contraindicated in pregnant women (Abortifacient)
KEY LEARNING POINTS: STUDY GUIDE

1. **Physiological effects of glucocorticoids**
   a) Carbohydrate and protein metabolism:
      *↑*hepatic gluconeogenesis, *↓*peripheral glucose uptake ⇒ *net ↑*blood glucose protects glucose-dependent tissues in times of stress
   b) Redistribution of Fat:
      *↓*Extremities, *↑*truncal obesity
   c) Cardiovascular system:
      *↑*glucocorticoids ⇒ hypertension; *↓*glucocorticoids ⇒ hypotension
   d) Inhibition of Immune and Inflammatory responses
   e) GI tract: *↑*gastric acid/pepsin synthesis
   f) Skeleton: *↑*bone loss
   g) CNS: *↑*mood elevation
   h) Feedback inhibition of the HPA axis:
      GC ⇒ *↓*CRH + *↓*ACTH production ⇒ *↓*cortisol production (Adrenal Atrophy)

2. **Physiological effects of mineralocorticoids**
   *↑*Aldosterone ⇒ *↑*Na+ reabsorption + *↑*extracellular fluid + *↑*alkalosis ⇒ **HYPERTENSION**
   *↓*Aldosterone ⇒ *↑*Na+ wasting + *↓*extracellular fluid + *↑*acidosis ⇒ **HYPOTENSION**

3. **Mechanism of action**
   a) Both glucocorticoids and mineralocorticoids mediate their biological responses by binding to specific receptors that are latent transcription factors.
   b) When bound by ligand these receptors translocate from the cytoplasm to the nucleus where they either activate or inhibit specific target genes.

4. **Cortisol synthesis and metabolism**
   a) Normal adults secrete 10-20 mg cortisol and 0.125 mg aldosterone per day
   b) Cortisol secretion is controlled by a circadian rhythm
      max @ 8am~16 mcg/dL
      min @ 11pm- midnight
   c) 11β hydroxysteroid dehydrogenase enzymes regulate the activity of cortisol in various tissues.
      - 11β HSD2 inactivates cortisol by converting it to cortisone in aldosterone-sensitive tissues such as kidney, salivary gland and colon- thereby preventing the more abundant cortisol from inappropriately activating mineralocorticoid receptors in these tissues
      - 11β HSD1 expressed in the liver converts cortisone back to the active cortisol

5. **Indications for glucocorticoids**
   (A) **HORMONE REPLACEMENT THERAPY**
   (i) Adrenal Insufficiency:
      Primary (Addison’s Disease)
      Secondary (suppression of HPA by exogenous GC)
Treatment

a) Hydrocortisone or prednisone/dexamethasone used for cortisol replacement
   Levels must be increased in setting of stress:
   e.g. illness, surgery & pregnancy

b) Fludrocortisone used for aldosterone replacement (not usually necessary in secondary disease)

(ii) Congenital Adrenal Hyperplasia
   - Enzyme defect in corticosteroid synthesis (e.g. CYP21)
   - ↓Cortisol ⇒ loss of HPA regulation ⇒ ↑ACTH ⇒ ↑adrenal hyperplasia ⇒
     ↑Androgens (due to build up of intermediate compounds that are shuttled into the androgen synthesis pathway)
   - Hypervirilization of female sex organs and adrenal crisis due to lack of cortisol/aldosterone production

Treatment

Prenatal - In utero dexamethasone treatment initiated < 9 wks gestation
   (Female only; for males treatment can be delayed until birth)
   - Inhibits ACTH and CRH production ⇒ ↓Androgen synthesis ⇒ suppresses female hypervirilization

Postnatal - lifelong hydrocortisone + fludrocortisone to prevent adrenal crisis

(B) NON-ENDOCRINE INDICATIONS FOR GLUCOCORTICOIDS

(i) Rheumatoid arthritis and related diseases
(ii) Allergies
(iii) Organ transplantation
(iv) Nephrotic syndrome
(v) Inflammatory conditions e.g. psoriasis, allergic conjunctivitis, IBD
(vi) Treatment of leukemia & lymphoma
(vii) Respiratory distress syndrome - in utero DEX treatment of at risk pregnancies
(viii) Cerebral edema - brain tumors, bacterial meningitis, HACE

6. Adverse Effects

A. ABRUPT WITHDRAWAL
   a) Disease flare up due to immune system rebound
   b) Acute adrenal insufficiency due to HPA suppression and Adrenal atrophy

B. SUPRAPHYSIOLOGICAL EFFECTS OF CHRONIC GLUCOCORTICOIDS
   a) Weight gain
   b) Facial plethora
   c) Diabetes
   d) Risk of infection
   e) Edema
   f) Hypertension
   g) Cardiovascular disease
   h) Myopathy
   i) Osteoporosis
   j) Peptic Ulcer
   k) Impaired wound healing
   l) Emotional disturbance/Euphoria
   m) Glaucoma/Cataracts
   n) Growth retardation in children

7. Cushing's Disease/Cushing's Syndrome
   Caused by chronic exposure to glucocorticoid activity (exogenous or endogenous)
**Symptoms:** truncal obesity, buffalo hump, facial plethora, easy bruising, thinning of the skin, purple striae on stomach, hypertension, hyperglycemia, muscle weakness, mental changes

**8. Treatment of Cushing's Disease**

a) Surgical tumor resection if possible

b) Cortisol synthesis inhibitors as adjunct to surgery, or if surgery is not possible
   - Ketoconazole (inhibits CYP11A1 & CYP11B1)
   - Etomidate (inhibits CYP11A1 & CYP11B1)
   - Metyrapone (inhibits CYP11B1 & aldosterone synthase) - safe in pregnancy

**GOAL:** To reduce elevated cortisol levels back towards the normal range by inhibiting enzymes involved in cortisol biosynthesis

Note: All patients will require careful monitoring of cortisol production to avoid adrenal crisis.

c) Mitotane
   - adrenolytic drug specifically destroys cortisol-producing adrenocortical cells
   - not safe in pregnancy
   - patients will ultimately require supplementation with hydrocortisone to prevent adrenal crisis (note: zona glomerulosa is spared)

d) Mifepristone
   - Progesterone receptor antagonist
   - antagonizes Glucocorticoid receptors at high doses
   - prevents excessive activation of GR in Cushing's
   - approved for treatment of refractory Cushing's

**Adverse Effects**

Can cause Adrenal Insufficiency (needs to be monitored)

Contraindicated in pregnant women (Abortifacient)
### Glucocorticoids and Adrenal corticosteroid synthesis inhibitors

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<td>Cerebral edema</td>
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### Ketaconazole
- **INDICATIONS**: Medical Treatment of Cushing’s Disease
- **MOA**: Inhibits CYP11A1/CYP11B1
- **ADVERSE EFFECTS**: ↑ Risk Adrenal Insufficiency

### Etomidate (i.v)
- **INDICATIONS**: Medical Treatment of Cushing’s Disease
- **MOA**: Inhibits CYP11A1/CYP11B1
- **ADVERSE EFFECTS**: ↑ Risk Adrenal Insufficiency

### Metyrapone
- **INDICATIONS**: Medical Treatment of Cushing’s Disease
- **MOA**: Inhibits CYP11B1/CYP11B2
- **ADVERSE EFFECTS**: Ablation of adrenocortical cells

### Mitotane
- **INDICATIONS**: Medical Treatment of Cushing’s Disease
- **MOA**: Inhibits CYP11B1/CYP11B2
- **ADVERSE EFFECTS**: Ablation of adrenocortical cells

### Mifepristone
- **INDICATIONS**: Medical Treatment of Cushing’s Disease
- **MOA**: Glucocorticoid R antagonist (@ high dose)
- **ADVERSE EFFECTS**: Ablation of adrenocortical cells
THYROID AND ANTITHYROID DRUGS

Date:

KEY CONCEPTS AND LEARNING OBJECTIVES

Thyroid hormone plays a major role in regulating development as well as metabolism and calorigenesis.

1) Describe the steps in the synthesis of the thyroid hormones: Tetraiodothyronine (T₄) and triiodothyronine (T₃)

2) Explain the endocrine regulation of T₃ and T₄ production and the role of feed-back loops

3) Discuss the physiological roles of T₃ and T₄ and the changes associated with hypo- and hyper-thyroidism.

4) List the indications, contraindications and clinical uses of the drugs used in the treatment of hypo- and hyper-thyroidism.

5) List the major adverse effects associated with the drugs used in the treatment of hypo- and hyper-thyroidism.

6) Discuss the mechanism of the action of drugs used to treat hyperthyroidism.

List of Drug: See Summary Table at the end of the hand out.
Thyroid Hormone:
Structure:

Synthesized in the thyroid gland. The intrathyroidal processing during synthesis of T\(_3\) and T\(_4\) is shown in the figure below.

1: Trapping of iodide at the basement membrane and passage to the apical cell surface.
2: Synthesis of the polypeptide chain of thyroglobulin (Tg).
3: Transport of newly synthesized thyroglobulin (Tg) to the apical surface in apical vesicals (AV).
4: Iodination of Tg by iodinium cation (I\(^+\)).
5: Retrieval of the Tg by micropinocytosis into small vesicles (MPV) or by massive engulfment.

Adapted from Human Pharmacology, 2\(^{nd}\) Edition
colloid droplets (CD).
6: Fusion of lysosomes (L) with CD and MPV, proteolysis of Tg (Cathepsins D, B & L) and dipeptidases to release of iodinated tyrosines, T₃ and T₄.
7: Release of T₃ and T₄ into the bloodstream.
8: Deiodination of DIT and MIT with recirculation of the iodide.

**Iodide Uptake:**
- active transport (energy dependent), against a 50 to 300-fold electrochemical gradient. (stimulated by TSH)
- Transport is from basement membrane to the apical cell surface.

**Synthesis of T₃ and T₄:**
- thyroid peroxidase catalyses the oxidation of I⁻ to iodinium (I⁺), followed by iodination of selected tyrosine residues on thyroglobulin (Tg).
- thyroglobulin (~600 kDa protein) is synthesized in the cells and secreted in the epithelial lumen.
- iodination of thyroglobulin produces mono- and diiodotyrosine.
- mono- and diiodotyrosine couple within the thyroglobulin to form T₃ and T₄.
- the thyroglobulin precursor is stored in the lumen as colloid.

**Release:**
- in response to TSH.
- reuptake of Tg into cells, followed by proteolytic degradation in lysosomes to release the T₃ and T₄.
- only T₄ and T₃ are released (approx. ratio: 4:1), remaining aminoacids, monoiodotyrosine are reutilized.

**Transport of T₃ and T₄:**
- transported bound to two main plasma protein
  1) thyroxine binding globulin
  2) Thyroxine binding prealbumin (transthyretin, T₄ only) and albumin (both T₃ and T₄)
- transport modulated by various clinical conditions and drugs
  - e.g. Renal Disease-proteinuria-decreased plasma protein concentration
  - Pregnancy and Estrogen Administration-increased plasma proteins and increased TBG - less free hormone!
  - Testosterone and Glucocorticoids decrease TBG levels
Possible Drug Interactions:
• Diphenylhydantoin displaces T₃ and T₄ binding to TBG- hyperthyroidism symptoms
• Salicylates displace T₃ and T₄ from albumin!
• affinity of T₄ for TBG and albumin much higher than T₃ -therefore higher percentage of T₃ unbound (~0.4%) as compared to T₄ (~0.04%)
• only free hormone is active
• T₃ more potent than T₄
• significant amount of T₄ is converted into T₃ in the periphery - liver, brain, pituitary.
• T₁/₂ of T₃ is approximate 1 day, 7 days for T₄ - end result circulating ratio of T₄:T₃ = 20:1

Mechanism of Action:
All cells respond to thyroid hormone (growth hormone-like action).
• several sites of action:
  (1) Hormone-receptor complex binds to the promoter region of many genes resulting in transcriptional regulation of gene expression. In some instances, mRNA may be stabilized. Increases GH transcripts and decreases TRH transcripts.
  (2) Increased lipolysis in adipose tissue and fat utilization for energy. In brown adipose tissue may uncouple ox-phos by inducing uncoupling protein synthesis - generating heat.
  (3) May also have a direct effect on glucose transporter of the Na/K ATPase.
• absolutely critical for mental development during early life - untreated hypothyroidism of newborn leads to cretinism.
• absolutely critical for the development of proper dentition.

Physiological Role of Thyroid Hormone:
1) Calorigenesis
• increase metabolic rate, oxygen consumption, appetite
• heat intolerance
2) Growth and Development
• essential for CNS development
• essential for skeleton and dental development
3) Cardiovascular
• increase rate and strength of heart beat, increase cardiac output - increase in α-MHC and myosin Ca²⁺ ATPase as well as β-AR
• increase arterial pressure
• hypersensitivity to catecholamines
4) Intermediary Metabolism
• stimulate glycogenolysis and gluconeogenesis (increase blood glucose)
• increased lipid catabolism (lower plasma cholesterol levels)
• net loss of protein mass

Thyroid Disorders:
The thyroid gland may secret too little or too much thyroid hormone resulting in
hypothyroidism and hyperthyroidism, respectively.

Hypothyroidism:
- Primary thyroid deficiency - usually referred to as myxedema, juvenile myxedema, cretinism, goiter (congenital or endemic)
  - Hashimoto’s thyroiditis (autoimmune disorders- Abs destroy the thyroid gland or decrease peroxidase or Tg-less common)
  - drug induced
  - congenital (no gland or ectopic) – one of the enzymes in synthesis is deficient
- Secondary thyroid deficiency - pituitary disease (TRH or TSH deficit can be radiation induced)

Treatment of hypothyroidism is easily achieved by administering pharmacological preparations of thyroid hormone (either thyroxine or triiodothyroxine) except in drug-induced hypothyroidism where the situation is corrected by withdrawing the offending drug.

Also used to treat myxedema coma (life-threatening, usually elderly population) & Nodular thyroid disease (negative feed-back on TSH release.

**Levothyroxine**
- Absorption is decreased by cholestyramine, iron & Ca^{2+} supplements, AIOH, and Soy products
- somewhat higher doses (per weight) are required in children
- may take several weeks to obtain steady-state levels
- monitor serum T\(_4\) and TSH levels
- Thyroxine increases the effect of warfarin, tricyclic antidepressants and amiodarone.
- Biliary excretion of T\(_4\) increased by drugs that increase CYP in liver- rifampicin, phenytoin, carbamazepine, oral contraceptives.

**Other preparations contain T\(_3\) alone (Liothyronine Na) for rapid onset of action as in Rx of Myxedema coma**

**OR mixture of T\(_3\) and T\(_4\) (liotrix) or thyroid gland extracts**

**Adverse Effects:** Dose related and symptom similar to hyperthyroidism – reduce dosage.

Hyperthyroidism:
- most common causes are Graves’ Disease (autoimmune thyroid disease also called exopthalamic goiter)
- toxic nodular goiter (carcinoma)

Graves’ Disease: Autoantibodies directed against receptors on thyroid gland stimulate the TSH receptors and stimulate thyroid hormone production. Optimum treatment - block immunogenic stimulation - this approach is currently impractical.
Treatment of hyperthyroidism is more complex and may consist of:
- surgery
- radioactive I
- drugs
  - thioureylenes
  - iodide
  - β-blockers
  - perchlorate (C1O4−)
  - corticosteroids
  - pertechnetate (TCO4−)

Corticosteroids decrease immune response and $T_4>T_3$

**Antithyroid Drugs:**

1) **Thioureylenes (thioamides)**
   - inhibit iodine organification (the peroxidase catalyzed reactions: iodination and coupling)
   - propylthiouracil (PTU) also inhibits peripheral conversion of $T_4$ to $T_3$
   - are rapidly absorbed, propylthiouracil has a shorter plasma half-life than methimazole
   - Methimazole ($t_{1/2}=4$-$6$h) is 10 times more potent than PTU ($t_{1/2}~75$min)
   - methimazole and PTU crosses the placental barrier and are concentrated in the fetal thyroid
   - PTU is preferred in pregnant patients or nursing mothers because of restricted placental transfer and limited excretion in milk
   - minimal number of patients experience adverse reactions (3-12% of patients): agranulocytosis (watch for sore throat as early sign), granulocytopenia (leukocyte counts recommended), skin rash, look out for hypothyroidism

2) **Iodide**
   - at high doses inhibits iodide uptake!
   - in large doses inhibits synthesis of iodothyrosine and iodothyronine and, therefore, hormone release. High intracellular concentrations of $\Gamma^-$ have to be attained.
   - valuable in treatment of thyroid storm
   - decreases vascularity, size, and fragility of the hyperplastic gland - valuable pre-operative
treatment
• not to be used prior to radioactive iodide treatment
• must be used in conjunction with other drugs since the patient may overcome the iodide block resulting in thyrotoxicosis

3) Radioactive Iodide
• Na\textsuperscript{131}I is administered orally (t\textsubscript{1/2}=8 d)
• concentrated in the thyroid gland, where $\beta$ and $\gamma$ radiation will, then in several weeks, destroy all or part of the tissue
• no evidence of any radiation-induced damage to any other tissues
• used in adults 35 years and older, but not in women of child bearing age

Disadvantage: Delayed hypothyroidism (overtreatment)
4) $\beta$-adrenergic Receptor Blockers:
- T\textsubscript{3} increase number of $\beta$-adrenergic receptors in the heart
- The heart becomes more sensitive to $\beta$-receptor stimulation – therefore increased heart rate and perhaps contractility
- $\beta$-blockers help against the adverse cardiac side effects of hyperthyroidism
- Decreases deiodination of T\textsubscript{4} to T\textsubscript{3}

5) Anion Inhibitors
• due to their toxicity and uncertain effects these are only used as diagnostic tools

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Thyroid Storm:

Acute, life threatening thyroid hormone induced hypermetabolic state in patients with thyrotoxicosis (may be initial presentation in undiagnosed patients).

Symptoms: Heat intolerance, diaphoresis (sweating), hyperpyrexia, tachycardia, high output heart failure, propensity to develop cardiac arrhythmias, irritability, restlessness, severe agitation, delirium, seizure, and coma.
GI: diarrhea, vomiting, jaundice, and abdominal pain.

**Causes of Thyroid Storm:**

Infection, surgery, trauma, radioactive iodide treatment, pregnancy, anti-cholinergic and adrenergic drugs, thyroid hormone ingestion, diabetic ketoacidosis.

3 to 5 times more common in females than in males.

**Treatment:**

Antipyretics (acetaminophen) to control fever
i.v hydrocortisone - block T4>T3 conversion and immunosuppressive
β-blockers - block T4>T3 conversion and cardiac actions
PTU - preferred since it blocks T4>T3 conversion
High doses of iodide to block thyroid hormone release
Treat heart failure, if necessary.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification</th>
<th>Mechanism Of Action</th>
<th>Routes of administration</th>
<th>Type of therapeutic use</th>
<th>Drug interactions</th>
<th>Major side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-T₄ (Levothyroxine-Na (L-T₄) (Synthroid, levoxyl, levothyroid, unithroid, etc.))</td>
<td>Thyroid Hormone (T₄)</td>
<td>Thyroid hormone replacement</td>
<td>1. Oral 2. injection</td>
<td>1. Hypothyroidism 2. Cretinism 3. TSH suppression therapy for thyroid cancer patients 4. Occasionally, same as (3) in nontoxic goiter</td>
<td>Increased biliary excretion of T4 with drugs that induce CYPs (e.g. phenytoin, rifampin, carbamazepine)</td>
<td>Those of hyperthyroidism (e.g. heat intolerance, agitation, etc.)</td>
<td>Narrow therapeutic window – FDA recommends checking bioavailability of different brands</td>
</tr>
<tr>
<td>Liothyronine – Na (L-T₃) (Cytomel, Triostat)</td>
<td>Thyroid Hormone (T₃)</td>
<td>Thyroid Hormone replacement</td>
<td>1. Oral 2. injection (Triostat)</td>
<td>1. Occasionally used for rapid onset of action or shorter lasting action e.g. myxedemic coma, prep for ¹³¹I therapy of thyroid cancer.</td>
<td>Same as above and perhaps greater frequency and intensity</td>
<td>Same as above and perhaps greater frequency and intensity</td>
<td>T₃ is more potent – therefore, may have more serious side effects such as cardiacarrhythmias</td>
</tr>
<tr>
<td>Liotrix – mixture of T₃ and T₄ (Thyrolar)</td>
<td>Thyroid Hormone (T₃ + T₄)</td>
<td>Thyroid Hormone Replacement</td>
<td>1. Oral</td>
<td>Same as L-T₄ above</td>
<td>Same as L-T₄ above</td>
<td>Same as L-T₄ above</td>
<td>Preferred in nursing mothers – v. little in milk</td>
</tr>
<tr>
<td>Methimazole (Tapazole)</td>
<td>Thiourylene</td>
<td>Inhibits iodination of tyrosyl and coupling of iodotyrosine residues on Thyroglobulin</td>
<td>1. Oral</td>
<td>Same as PTU above</td>
<td>Same as PTU but agranulocytosis is dose-dependent</td>
<td>Same as above and perhaps greater frequency and intensity</td>
<td>Can be used in pregnant patients with same precautions as PTU</td>
</tr>
</tbody>
</table>

**SUMMARY REVIEW TABLE FOR LECTURE**
| Drug          | Classification | Mechanism Of Action                                                                 | Routes of administration | Type of therapeutic use            | Drug interactions                                                                 | Major side effects                                                                 | Comments                                                                                           |
|--------------|----------------|------------------------------------------------------------------------------------|--------------------------|------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Iodide       | Ionic inhibitor| High [iodide] inhibit uptake of I, iodination and coupling of tyrosyl residues on thyroglobulin and also inhibit release of Thyroid hormone. | 1. Oral 2. i.v. 3. injection | 1. preop- Rx of hyperthyroid state. 2. Thyroid storm 3. Prophylactic in protect against radioactive Iodide exposure | Not prior to ¹³¹I treatment – makes radioactive iodide ineffective | Hypersensitivity to i.v. dosing - angioedema                                                                 | Effects wane over time and thus, must be used in conjunction with other drugs                        |
| ¹³¹Iodide     | Ionic inhibitor| Concentrates in the thyroid gland and the beta and gamma radiation kill cells in immediate vicinity | 1. Oral                  | Ablation therapy for hyperthyroidism | High dose iodide                                                                   | Overtreatment – can produce hypothyroidism                                                                 | Absolutely contraindicated in Pregnancy. Adjucant therapy with beta-blockers of other drugs OK while awaiting full effectiveness |
| β- adrenergic receptor blockers | β-blockers | 1. block β-adrenergic receptors in CV system – decrease, HR, contractility, arrythmias, etc 2. inhibit deiodination – conversion of T4 to T3 | 1. oral                  | 1. Thyroid strom 2. adjuvant to ¹³¹I 3. acute treatment of hyperthyroid state | See autonomies lecture                                                                 | See autonomies lecture                                                                                     | Do not change thyroid hormone levels – changes clinical outcome                                      |
CALCIUM METABOLISM

**Reading Assignment:** Katzung 11th Edition, Chapter 42, pp. 753-772

**KEY CONCEPTS AND LEARNING OBJECTIVES**

Calcium is the fifth most abundant element in the body and plays major roles in the regulation of several physiological and pathological conditions.

1. Explain the role of the key organs involved in regulation of plasma calcium concentration

2. Discuss the endocrine regulation of calcium homeostasis and the mechanisms involved

3. State the principles underlying the treatment of hyper- and hypo-calcemia.

4. List the drugs used in the therapy of hypo- and hyper-calcemia.

5. List the indications, contraindications and clinical uses of drugs used in the therapy of hypo- and hyper-calcemia

6. Discuss the therapeutic uses of vitamin D, calcitonin, bisphosphonates, estrogen, and glucocorticoids in the maintenance of calcium homeostasis.

7. Describe the mechanism of action and clinical effects of the major drugs used in the maintenance of calcium homeostasis

**List of Drugs:** See summary Table at end of the handout
CALCIUM METABOLISM

PARATHYROID, CALCITONIN AND VITAMIN D

Calcium Regulation:

- Fifth most abundant element in the body, mostly in bones
- Essential for muscle contraction, cardiac function, maintenance of membrane integrity, blood coagulation, mediation of intracellular action of numerous hormones
- Organs involved in Ca\(^{2+}\) regulation: Kidneys, Intestine, Bone

Hypocalcemia: neuromuscular
tetany, muscle cramps, convulsions, laryngospasm

Rickets (inadequate bones mineralization during development)

Osteomalacia (inadequate bone mineralization in adult). Associated with

1. Inadequate dietary Ca\(^{2+}\) and/or vitamin D
2. Malabsorption due to defect in vitamin D activation
3. Malabsorption due to end-organ resistance to vitamin D
4. Hypoparathyroidism
5. Renal failure

-usually treated with vitamin D and Ca\(^{2+}\)
Hypercalcemia

Can result in cardiac arrhythmias (life threatening), renal damage (stone), soft tissue calcification, CNS abnormalities.

- more diverse in nature & etiology (e.g. hyperparathyroidism, hypervitaminosis D, sarcoidosis, neoplasia, hyperthyroidism, etc.); treatment depends on disease etiology and severity of condition

- usually treated with fluids, low Ca^{2+} diets, loop diuretics, glucocorticoids, sulfate, calcitonin, antiinflammatory agents, anticancer drugs

Vitamin D

- can be considered as a hormone; synthesized in skin (under ideal conditions, not required in diet), transported by blood to target tissues where it is activated, and binds to specific receptors

- vitamin D$_2$ is produced by u.v. irradiation-elicited activation of ergosterol in yeast and fungi

- vitamin D$_3$ (cholecalciferol) is produced similarly from 7-dehydrocholesterol in animals and higher plants

- vitamin D$_2$ and vitamin D$_3$ are not biologically active but both are equally good “prohormones” in the human

- initial activation of vit. D$_2$/D$_3$ occurs in the liver to form 25-hydroxy vit. D (calcifediol)

- final hydroxylation takes place in the kidney and is stimulated by parathyroid hormone and low phosphate; product is the most potent form of vit. D: 1,25-dihydroxy vit. D (calcitrol)

High Ca$^{2+}$ directly inhibits 1 hydroxylase and indirectly by decreasing PTH secretion - same for 1,25- di(OH) D (inhibits transcription of PTH).

Potency: Vitamin D$_3$ < 25-hydroxy D < 1,25 di-hydroxy D

- binds to receptors (similar to steroid receptors) which then alter transcriptional regulation of genes;
increases calbindins (Ca\(^{2+}\) absorption); more rapid effects likely due to effects at different levels also seen

- active vit. D (25-hydroxy and 1,25-dihydroxy) increase serum Ca\(^{2+}\) by increasing absorption of Ca\(^{2+}\) and phosphate from the intestine

- increase in serum Ca\(^{2+}\) and phosphate leads to bone mineralization (antirachitic effect)

- will also stimulate Ca\(^{2+}\) mobilization from the bone directly if dietary supplement of Ca\(^{2+}\) is inadequate. Stimulates osteoblasts on the bone that then activate osteoclasts to cause bone resorption - increasing Ca\(^{2+}\) and PO\(_4\)\(^{3-}\). (RANKL - osteoclast activation & Osteocalcin-osteoblast differentiation)

**Therapeutic Uses:**

1. Prophylaxis and cure of nutritional rickets (inadequate sunlight or diet)
2. Treatment of metabolic rickets and osteomalacia (inadequate bone deposition) in chronic renal failure
3. Treatment of hypoparathyroidism
4. Prevention and treatment of Osteoporosis

Several derivatives for specialized use: Calcipotiol – topical use for psoriasis, Paricalcitol (synthetic D\(_2\)) – i.v. infusion for secondary hyperparathyroidism.

**Drug Interactions:**

1) Estrogen, isonazide (TB drug), thiazide diuretics increase vit D levels – Estrogen effect desirable in osteoporosis treatment.
2) Ca Channel blockers (verapamil) decrease vit D synthesis
3) Cholestyramine decreases vit D. absorption
4) Phenobarbital, phenytoin, increase vit D metabolism
5) Antacids –over long term alter vit D. metabolism/bioavailability
Parathyroid Hormone (PTH)

- 84 amino acid polypeptide synthesized in the parathyroid gland attached to the thyroid gland
- binds to specific plasma membrane receptors and activates adenylyl cyclase
- acts directly on the kidneys to stimulate renal tubular reabsorption of Ca\(^{2+}\) and increases formation of 1,25-dihydroxy vit. D from 25-hydroxy precursor; also decreases phosphate reabsorption from kidney
- stimulates Ca\(^{2+}\) resorption from the bone (RANKL)
- indirectly enhances dietary Ca\(^{2+}\) absorption by increasing the formation of 1,25 dihydroxy vit.D

A PTH related protein is produced by several types of tumor cells- leading to hypercalcimia - may be involved in regular Ca metabolism in mammary gland and placenta.

PTH is used diagnostically to examine cAMP production by the kidneys (as monitored in urine), to detect pseudohypoparathyroidism (resistance to hormone).

PTH has very short half-life and until recently used only as diagnostic tool.

However since intermittent administration of PTH has been shown to increase bone deposition - **Recombinant Human PTH (1-34) Teriparatide (Forteo®):** used for treatment of severe osteoporosis – increases bone formation

- only available in injectible form

combination with alendronate may synergistically increase efficacy.

Not useful in treatment of hypoparathyroidism (short t\(_{1/2}\)
**Adverse Effects & Contraindications:** Osteosarcoma in animal model but – no human data but contraindicated in patients with increased risk of osteosarcoma (e.g. Paget’s disease with elevated Alkaline Phosphatase, open epiphyses, or prior skeletal radiation therapy)

- also not approved for use in children

- hypoparathyroidism is best treated by vitamin D and dietary Ca$^{2+}$

- hyperparathyroidism is usually treated by surgical resection of the gland; if surgery is contraindicated, low Ca$^{2+}$ and lots of fluid are indicated.

**Calcimimetics**

*Cinacalcet* activates the Ca$^{2+}$ sensing receptor (CaR) which has greatest conc. in the parathyroid gland. Activation of CaR inhibits PTH release

**Indications:** 2° hyperparathyroidism, parathyroid carcinoma, chronic kidney disease.

**Drug Interactions:** Metabolized by CYPs - therefore, certain drugs (ketoconazole, itraconazole, erythromycin) increase Cinacalcet conc.

Cinacalcet can increase conc of other CYP substrates e.g. Desipramine.

**Adverse reactions:** Hypocalcemia - check serum Ca closely

**Calcitonin**

- 32 amino acid polypeptide synthesized by the parafollicular cells of the thyroid. Secretion is regulated by plasma Ca$^{2+}$ levels; high Ca$^{2+}$ stimulates release of calcitonin

**Actions:** (generally opposite of those of PTH)

- decreases absorption of Ca$^{2+}$ from intestine

- increases urinary excretion of Ca$^{2+}$, Na$^+$, Mg$^{2+}$, Cl$^-$, and PO$_4$$^{3-}$

- inhibits osteoclast activity - resulting in decreased bone resorption and therefore, increased deposition - this leads to decreased plasma Ca$^{2+}$ concentration

**Therapeutic Use**
Human synthetic calcitonin (Cibacalcin) or salmon calcitonin (Calcimar or Miacalcin) can be
administered IM, sub q., or by nasal spray to treat the following conditions.

1. Used in treatment of Paget’s Disease (abnormal bone turnover), recently approved for
osteopenosis and less frequently in hypercalcemia associated with malignancy (osteolytic bone
metastasis) - more usual treatment with sulfate, EDTA, furosemide, ethacrynic acid,
gluocorticoids, and antineoplastic drugs (pli
camycin) (NOT PHOSPHATE - causes metastatic
calcification in soft tissues). Also low Ca
diet and fluids are indicated.
2. Used in osteoperosis to decrease bone resorption and diminish the chances of fractures
3. Useful in vit. D intoxication

Adverse Effects:
- hypersensitivity reactions (allergic reactions), nausea
- “escape” a major problem: loss of effectiveness especially of actions at the bone tissue

**Gallium Nitrate:** Gallium nitrate has been approved by the FDA for treatment of hypercalcemia of malignancy.
- decreases bone resorption

**Drug Interactions** with numerous drugs - antibiotics, anti-fungals, immunosuppresives.

**Adverse Effects:** Nephrotoxic – patients should be well hydrated and have good renal function.

**Glucocorticoids:**

Antagonizes the actions of vitamin D to increase absorption of Ca\(^{2+}\) from GI tract. Increases
urinary excretion of Ca\(^{2+}\).

Therefore, used in treatment of hypercalcemia associated with sarciodosis, malignancies or Vit.
D intoxication. Not particularly effective in PTH induced hypercalcemia – so differentiate
cause.

**Adverse Effects:** Should be used for intermittent treatment since long term- treatment can result
in osteoperosis. Also remember the suppression of the hypothalamic-adrenal axis.

**Thiazides:** Used for renal hypercalciuria
- Site of action – early segment of distal convoluted tubules in the kidneys
- Inhibits renal stone formation by increasing renal reabsorption of calcium from the lumen
  of the tubules.

**Denosumab:** Monoclonal Ab against RANKL – Binds RANKL and mimics action of
Osteoprotegerin. Approved for use in post-menopausal women at risk for osteopenosis (Prolia®)
and for preventing osteolysis from metastatic solid tumors (Xgeva®).
**Adverse Effects:** Urinary & respiratory tract infections probably because of role of RANKL in the immune system (T Helper cells express RANKL – maturation of dendritic cells). Constipation, rashes, & eczema from skin infections.

**Contraindications:** Not indicated in hypocalcemic patients. Ca\(^{2+}\) and Vitamin D should be sufficient before starting therapy with Denosumab.

**Bisphosphonates:**

Used in the treatment of bone diseases involving excessive bone destruction or resorption, e.g. Paget's disease, tumor-associated osteolysis, post-menopausal osteoporosis.

Act by adsorbing to bone crystals making bone resistant to enzymatic hydrolysis. Inhibits activity of osteoclasts that manage to ingest bisphosphonate-containing bone.

**Structure is similar to pyrophosphate.**

Pyrophosphate consists of two phosphate groups linked by an oxygen atom (P-O-P)

bisphosphonates have two phosphate groups linked by a carbon atom (P-C-P)

like pyrophosphate, bisphosphonates have very high affinity for calcium and therefore target to bone mineral in vivo.

Also inhibit production of 1,25-di-OH vit D – Adv. in Rx of Hypercalcemia due to Paget’s Disease.

**Etidronate - Didronel®, Didronel® IV**

Used to treat Paget’s Disease and hypercalcemia

- Pharmacokinetics
  - poorly absorbed (decreased with food)
  - distributes readily and concentrates in bone
  - excreted by kidneys; not metabolized
  - plasma elimination half-life - 6 hr
  - retention half-life in bone - 3-6 months

- Administration - oral (for Paget’s Disease); i.v. (for hypercalcemia)
- Not approved for osteoporosis.

- Contraindications/precautions
  - children, pregnancy, breast-feeding colitis
- pregnancy
- renal impairment

- Interactions
  - aluminum hydroxide
  - antacids
  - calcium salts, magnesium salts
  - iron salts

- Adverse effects
  - bone pain
  - adverse GI effects- dysphagia, pain, etc.
  - hypocalcemia, osteomalacia
  - metallic taste

**Pamidronate B Aredia®**

- Pharmacokinetics
  - poorly absorbed or tolerated orally
  - concentrates in bone - biphasic disposition
  - half-life - 2.1 hr; β half-life - 28 hr
  - excreted by kidneys; not metabolized
  - plasma elimination half-life - 6 hr
- Administration: i.v.

- Contraindications/precautions
  - children, pregnancy, breast-feeding
  - renal impairment

- Interactions
  - no drug interactions

- Adverse effects
  - bone pain, abdominal pain
  - anorexia
  - dyspepsia
  - fever
  - hypocalcemia, hypokalemia

**Alendronate - Fosamax®**

- Pharmacokinetics
- poor oral absorption
- transient distribution to soft tissue, with rapid redistribution to bone
- 78% protein bound
- excreted unchanged in urine
- half-life in bone - 10 years

Approved for treatment of osteoporosis – particularly useful in women who cannot tolerate estrogen

• Administration - oral or i.v.

• Contraindications/precautions
  - children, pregnancy, breast-feeding
  - dysphagia
  - GI disease, esophagitis, gastritis
  - hypocalcemia
  - renal impairment
  - vitamin D deficiency

• Interactions
  - aluminum hydroxide
  - antacids
  - calcium salts, iron salts, magnesium salts
  - NSAIDs, ranitidine, salicylates - ulcerations

• Adverse effects
  - abdominal pain, constipation, diarrhea
  - bone pain
  - dysphagia
  - esophageal ulceration, esophagitis, gastritis
  - headache
  - hypocalcemia, hypophosphatemia

Newer Bisphosphonates: Risedronate and Tiludronate

Risedronate is approved for use in osteoporosis.

Main Characteristics of Bisphosphonates:

1) Pharmacokinetics: Poor absorption when orally administered
  - decreased further by food!
  - short plasma half-life, but half-life after deposition in bone long - 3/6 mths
etidronate - >10 yrs alendronate

2) Contraindication: Children, pregnancy, breast feeding, GI ulcers, decreased renal function.

3) Drug Interactions: Al(OH)₃, Antacids, Ca, Mg, Fe salts, NSAIDs - None with Pamlidronate (i.v.)

4) Adverse Effects: Bone pain, GI- dyspepsia, anorexia, esophageal ulcerations, hypocalcemia, hypophosphatemia

5) Indications: Paget’s disease, Osteoperosis - alendronate, risendronate, ibandronate

6) Other effects: decreased production of 1, 25 di(OH) D decreased intestinal transport of Ca.

**Fluoride**

- **Mechanism of Action**
  - mitogen for osteoblasts to stimulate bone formation

- **Indications: Prophylaxis of dental caries**

- **Pharmacokinetics**
  - absorption from GI tract is rapid and complete
  - stored in bones and teeth
  - ion is pharmacologically active form
  - renal excretion, 90% filtered by glomerulus; reabsorption by tubules

- **Administration**
  - oral
  - topical to oral cavity preferably during teething in children

- **Contraindications/precautions**
  - arthralgia
  - pregnancy, breast-feeding, children
  - dental fluorosis B mottled enamel, small paper white opaque areas scattered over the enamel - in extreme cases deep brown or black stains on the enamel

- **Adverse effects**
  - dermatitis
  - fluorosis
- GI bleeding, nausea/vomiting
- stomatitis, urticaria

**Estrogen:** Used in postmenopausal women to prevent osteoporosis
- increases risk of endometrial carcinoma. However combined with progestins decreases this risk – combination of estrogen and progestins may cause menstruation again
- probably works by decreasing the actions of PTH to increase bone resorption (increase osteoprotegrin from osteoblasts - inhib RANK on Osteoclasts)
- also increases 1,25-di-OH vit D probably by decreasing serum phosphate
- may also have direct actions on bone remodeling.

**Specific Estrogen Receptor Modulators (Raloxifene – 1st approved FDA SERM):** Estrogen agonist in bone but estrogen antagonist in breast and uterine tissues (also in brain – causes hot flashes).

Raloxifene *(Evista).* First SERM to be approved for preventing spinal fractures. (Does not appear to have any protective effect on other fractures, including those in the hip.)

Raloxifene does not effect ovulation and may be an option for women at risk for osteoporosis who are still menstruating, but should not be used in pregnant or breast-feeding women.

Raloxifene also increases risk for deep vein thrombosis, in which clots form in the large veins of the legs.

**Newer SERMs:** lasofoxifene and bazedoxifene – reduced breast cancer risk
### SUMMARY REVIEW TABLE FOR LECTURE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Forms available</th>
<th>Mechanism of Action</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>1. Calcitriol 2. Doxercalciferol (hypoparathyroidism) 3. 1α-hydroxycholecalciferol already OH in 1 postion (renal osteodystrophy) 4. also see under comments</td>
<td>Increases Ca and PO₄ absorption from GI Increases bone resorption if dietary Ca intake low.</td>
<td>1. Oral 2. parenteral</td>
<td>1. Prophylaxis 2. nutritional rickets 3. metabolic rickets and osteomalacia in chronic renal failure 4. prevention and Rx of osteoporosis 5. hypoparathyroidism</td>
<td>1. Estrogen, isonazide (TB drug), thiazide diuretics increase vitamin D levels – estrogen effect desirable in postmenopausal women on hormone replacement 2. Ca channel blockers (verapamil) may decrease vit D synthesis 3. Cholestyramine – decrease vit D absorption 4. Phenobarb, phenytoin – increase vit D metabolism 5. Antacids (long term) alter metabolism/bioavailability of vit D.</td>
<td>Those of hypercalcemia – decrease dose</td>
<td>Several derivatives available for special use: e.g. Calcipotriol used topically for psoriasis, Paricalcitol synthetic D₂ given i.v. for 2° parathyroidism</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
<td>Teriparatide (recombinant human PTH (1-34))</td>
<td>Although PTH causes bone resorption, intermittent injections (once/day) enhance bone deposition. Note: Only teriparatide is described above but you should also know that mechanism of action of PTH and its role in Ca homeostasis.</td>
<td>1. injection</td>
<td>1. severe osteoporosis</td>
<td></td>
<td></td>
<td>Contraindiated when risk for osteosarcoma, (e.g. paget’s disease with high alk. Phtase, open epiphyses, or prior radiation of skeleton). Given with Alendronate - synergistic action.</td>
</tr>
<tr>
<td>Cacitonin</td>
<td>Human synthetic – Cibacalcin Salmon – Miacalcin, Calcimar</td>
<td>Decreases absorb of Ca from intestine. Increases urinary excretion of Ca, Na, Mg, Cl, &amp; PO₄. Inhibits osteoclast activity – decrease bone resorption &amp; increased deposition All of the above lower Plasma Ca.</td>
<td>1. injection 2. nasal spray</td>
<td>1. Paget’s disease 2. osteoporosis 3. Vit D intoxication 4. less frequently in hypercalcemia of malignancy</td>
<td></td>
<td>Hypersensitivity reactions</td>
<td>“Escape” – lack of effectiveness at the level of bone over time problematic</td>
</tr>
<tr>
<td>Drug</td>
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<tr>
<td>Gallium nitrate</td>
<td>Ganite</td>
<td>Inhibits bone resorption</td>
<td>1. injection</td>
<td>1. hypercalcemia of malignancy</td>
<td>Too numerous to list here but include antibiotics, anti-fungals, immunosuppressives - look out for nephrotoxicity</td>
<td>1. Nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Hydrocortisone</td>
<td>Antagonize the actions of Vit D. Decrease Ca absorption from intestine, Increase urinary Ca excretion</td>
<td>1. Oral 2. i.v.</td>
<td>1. Vit D intoxication 2. hypercalcemia of malignancy</td>
<td>Refer to glucocorticoid lecture</td>
<td>Intermittent treatment only – long term use causes osteoporosis and inhibits HPA axis</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>Prolia® (osteo) Xgeva® (osteolysis)</td>
<td>Monoclonal Ab against RANKL</td>
<td>subq injection</td>
<td>osteoporosis in pm women osteolysis from solid tumor bone metastasis</td>
<td>Ca lowering drugs</td>
<td>Urinary &amp; respiratory tract infections. Skin rash, eczema.</td>
<td></td>
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<tr>
<td>Bisphosphonates</td>
<td>Etidronate, Pamidronate, Alendronate Risedronate, Tiludronate</td>
<td>Adsorbed to bone crystal making it resistant to enzymatic hydrolysis.</td>
<td>1. Oral 2. injections (Pamidronate)</td>
<td>1. Paget’s disease 2. Osteoporosis 3. Hypercalcemia of malignancy</td>
<td>Al(OH)₃, Antacids, Ca, Mg, Fe salts, reduce absorption NSAIDs- increased incidence of GI ulcers None with Palmidronate</td>
<td>Bone pain, GI dyspepsia, anorexia, esophageal ulceration, hypocalcemia, hypophosphatemia</td>
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<td></td>
<td>Poorly absorbed – given on empty stomach. Short plasma half-life BUT long half-life after bone deposition – 3 mths to 10 yrs.</td>
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<td></td>
<td><strong>Contraindicated in:</strong> children, pregnancy, breast feeding, GI ulcers, renal insufficiency</td>
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<td>Alendronate + teriparatide may act synergistically</td>
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<tr>
<td>Calcium sensor mimetics</td>
<td>Cinacalcet</td>
<td>Mimics Ca on the Ca sensing receptors to inhibit PTH secretion by parathyroid</td>
<td>1. Oral</td>
<td>1. 2° hyperparathyroidism 2. parathyroid carcinoma 3. chronic renal disease</td>
<td>Metabolized by different CYPs. Ketoconazole, erythromycin, itraconazole increase levels of Cinacalcet Can increase conc of other CYP metabolized drugs, e.g. desipramine</td>
<td>Hypocalcemia - Check serum Ca levels closely and regularly</td>
<td></td>
</tr>
</tbody>
</table>
| Estrogen & SERMs            | Raloxifene (SERM) | **Estrogen**: Inhibit actions of PTH at bone? Increases 1,25 diOH vit D by decreasing serum PO₄  
**SERMs**: Estrogen antagonists in breast and estrogen agonists in bone | 1. oral                  | 1. Osteoporosis in postmenopausal women. 2. Osteoporosis in menstruating women – **Raloxifene only** | See estrogen lecture                                                                 | Hot flashes, deep vein thrombosis, etc See estrogen lecture | Increased risk of endometrial cancer with estrogen – not SERMs Raloxiphene not indicated in pregnancy and breast-feeding |