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American College of Clinical Pharmacy

Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Diabetes Mellitus

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Learning Objectives

1. Demonstrate an understanding of the normal regulation of blood glucose with respect to the actions of insulin, cortisol, growth hormone, glucagon, and incretins in glucose homeostasis.
2. Identify differences between prediabetes, type 1 diabetes mellitus (DM), type 2 DM, and gestational diabetes, including differences in diagnostic criteria and clinical presentation.
3. Explain sick-day rules for a patient with diabetes.
4. Compare agents used in the treatment of DM, including mechanisms of action, adverse effects, contraindications, and overall effectiveness.
5. Select appropriate insulin regimens for patients based on desired onset, peak, and duration of insulin effects.
6. Individualize a comprehensive glycemic treatment and monitoring plan for a patient with DM.
7. State appropriate lipid and blood pressure targets for patients with DM.
8. Discuss short-term and long-term complications associated with diabetes as well as strategies to prevent or slow their progression.

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Clinical Pearls

- Insulin decreases glucose; all other hormones increase blood glucose.
- Diabetes management: It is all about the food!
- The bigger they are (A1C), the harder they fall.
- With oral therapy, add, do not substitute, therapies.
- Diabetes management: It is more than just (treating) blood glucose.
- Diabetes is a CV disease risk equivalent.
- Fix the fasting (glucose) first.
- Fifty percent of patients with type 2 DM present with end-organ damage at the time of diagnosis.

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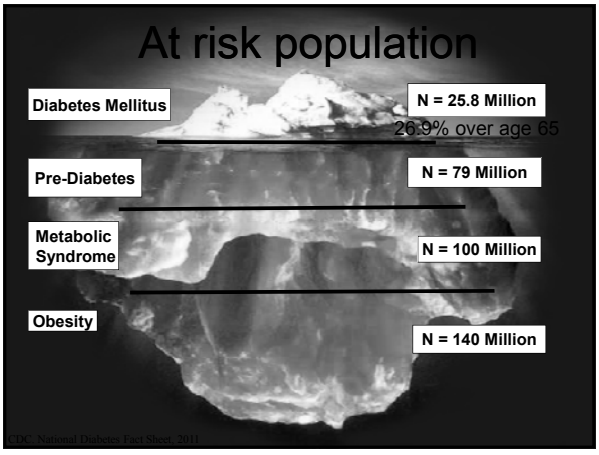
At risk population



CDC. National Diabetes Fact Sheet. 2011

The Ticking Clock Hypothesis

- Type 2 DM is associated with microvascular and macrovascular complications.
- Duration of DM and severity of glycemia are primarily associated with microvascular disease.
- Metabolic disturbances during the prediabetic period may contribute to macrovascular disease.
- Macrovascular complications: the clock starts ticking years before the onset of clinical diabetes.

Haffner SM et al. JAMA. 1990;263:2893-8.

The Endothelium and Insulin Resistance

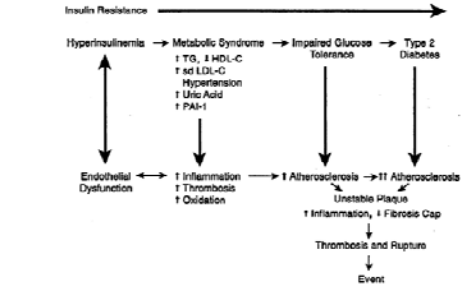
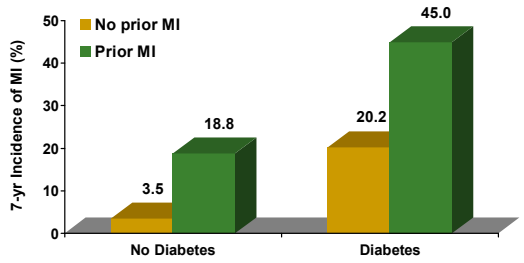


FIGURE 3. The progression of insulin resistance to diabetes appears to parallel the progression of endothelial dysfunction to atherosclerosis and cardiovascular events. HDL-C = high-density lipoprotein cholesterol; PAI-1 = plasminogen activator inhibitor–1; sd LDL-C = small, dense low-density lipoprotein cholesterol; TG = triglycerides.

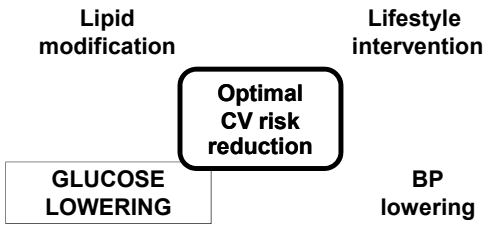
Hsueh WS, Quinones MJ. Am J Cardiol. 2003;92:3J-9J.

Diabetes Is a CHD Risk Equivalent



Haffner SM et al. N Engl J Med. 1998;339:229.

Benefit of multifactorial interventions



The ABC's of Diabetes

- A1C (and ASA)
  - < 7.0% (ACE < 6.5%)
- Blood Pressure
  - < 130/80 mmHg (125/75 mmHg)
- Cholesterol (and Cessation of smoking)
  - LDL-C < 100 mg/dL (<70 mg/dL?)
  - Non-HDL-C < 130 mg/dL (<100 mg/dL?)
  - HDL-C > 40 mg/dL (> 50 mg/dL in women)
  - TG's < 150 mg/dL

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ADA Diabetes Classification

- Type 1 Diabetes
  - Autoimmune Beta-cell destruction (includes LADA or Type 1 ½ DM)
  - Previously known as IDDM, juvenile onset, and ketosis prone diabetes
- Type 2 Diabetes
  - Progressive insulin secretory defect in the face of insulin resistance
  - Previously known as NIDDM, and adult onset diabetes
  - Makes up 90-95% of all diabetes cases, multiple RF's
  - Diabetes-related complication found in 50% at Dx

ADA. Diabetes Care 1997; 20:1183-97.

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ADA Diabetes Classification

- Gestational Diabetes Mellitus
  - Onset of diabetes during pregnancy; 200,000^{+}/year
- Other Specific Types
  - Genetic Defects (includes MODY)
  - Exocrine pancreatic disease
  - Endocrinopathies
  - Drug/Chemical Induced
- Additional Terms
  - Type 1 ½ diabetes (LADA)
  - MODY
  - Double-double diabetes

ADA. Diabetes Care 1997; 20:1183-97.

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ADA 1997 Diagnostic Guidelines

- Symptoms of diabetes with casual Plasma Glucose ≥200 mg/dL
- Fasting Plasma Glucose ≥126 mg/dL*
- 2 hr Plasma Glucose ≥200 mg/dL (after a 75-g OGTT)*

* Should be confirmed by repeat testing on a different day

ADA. Diabetes Care 1997; 20:1183-97.

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A1C as Diagnostic Criteria for Diabetes Mellitus (2010)

- A1C ≥ 6.5%
- A1C performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial reference assay.
- Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes.

ADA. Diabetes Care. 2010;33:S12-S61.

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Diagnosis of Gestational Diabetes (2011)

- Screen between weeks 24 and 28 of gestation if no diabetes risk factors
- Screen at first prenatal visit in patient with even one diabetes risk factor, and if normal, repeat between weeks 24 and 28
- Two-step screening is no longer recommended
- One abnormal blood glucose result makes the diagnosis

75-g Glucose Tolerance Test:	Cutoffs
Fasting	92 mg/dL
1-hour	180 mg/dL
2-hour	153 mg/dL

- Women with a history of GDM should be screened for diabetes 6-12 weeks postpartum using non-pregnant OGTT criteria

ADA. Diabetes Care. 2011;34:S11-S61.

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Patient Case #1

An obese 50-year-old Hispanic American woman with a history of gestational DM presents to the clinic for her annual physical examination. Her family history is significant for type 2 DM in her parents, both sets of grandparents, and several aunts and uncles. A FPG is 160 mg/dL. She has no concerns. Which one of the following best conveys how this patient's treatment should be managed?

A. Rescreen in 3 years.
B. Obtain another FPG level next week
C. Order an OGTT before she leaves her appointment
D. Diagnose type 2 DM and initiate LS changes

Workbook Page 1-140; Answer: Page 1-168

Patient Case #1

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Workbook Page 1-140; Answer: Page 1-168

Prediabetes

- Hyperglycemia that does not meet diagnostic threshold for DM
  - Impaired Fasting Glucose (IFG): 100-125 mg/dl
  - Impaired Glucose Tolerance (IGT): 140-199 mg/dl 2 hours after a 75g oral glucose load
  - A1C: 5.7-6.4%

ADA. Standards of Medical Care in Diabetes. Diabetes Care 2012;35(S1):S11-S63.

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Interventions for the Prevention of Diabetes in Patients with Prediabetes

- Weight loss of 7%
- Increase in physical activity to at least 150 minutes/week of moderate activity (such as walking). Follow-up counseling appears to be important for success
- Drug Therapy
  - Metformin
  - α-Glucosidase inhibitors
  - Orlistat
  - TZD
- Monitor for development of DM annually

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Prevention of Type 2 Diabetes: Completed Trials in IGT or GDM

Trial	Journal/Year	Treatment	Results (Risk reduction)
Da Qing IGT and Diabetes Study	*Diabetes Care* 1997	Diet +/or exercise	31%-46%
Finnish Prevention Study (FPS)	*N Engl J Med* 2001	Intensive lifestyle	58%
Diabetes Prevention Program (DPP)	*N Engl J Med* 2002	Metformin	31%
		Lifestyle changes	58%
		Troglitazone	23%
STOP-NIDDM	*Lancet* 2002	Acarbose	25%
TRIPOD	*Diabetes 2002*	Troglitazone	55%
XENDOS	*Diabetes Care 2004*	Orlistat	37%
DREAM	*Lancet 2006*	Rosiglitazone	60%
ACT NOW	*N Engl J Med* 2011	Pioglitazone	72%

Type 1 Diabetes PATHOPHYSIOLOGY

- Autoimmune B-cell Destruction
  - Islet cell cytoplasmic autoantibodies
  - Insulin autoantibodies
  - Antibodies to glutamic acid decarboxylase . (GAD)
- Loss of Insulin Secretion
  - Molecular mimicry model
  - Direct environmental toxin

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Type 2 Diabetes PATHOPHYSIOLOGY

- Insulin Resistance
- Relative insulin deficiency
- Increased hepatic glucose production
- Neuroendocrine dysfunction
  - Decreased amylin secretion
  - Impaired incretin effect
- Increased gastric emptying rate

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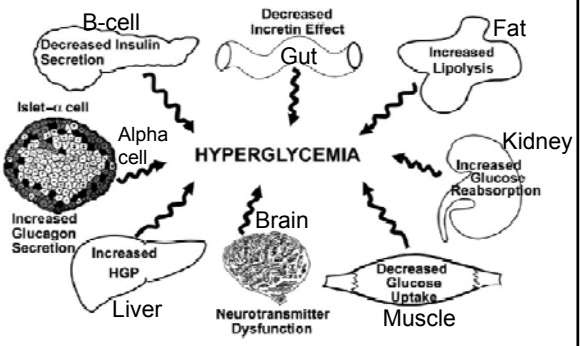
BANTING LECTURE

From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

Ralph A. DeFronzo

DeFronzo RA. Diabetes. 2009;58:773-95.

The Ominous Octet



DeFronzo RA. Diabetes. 2009;58:773-95.

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General Goals of Therapy

- Eliminate symptoms
- Avoid hypoglycemia
- Achieve/maintain IBW
- Normalize growth/development
- Prevent long-term complications
- Obtain Glycemic Goals

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Glycemic Goals of Therapy in Diabetes

Goal	ADA	AACE
A1C	< 7%*	≤ 6.5%
Premeal plasma glucose (mg/dL)	70-130	< 110
Postprandial plasma glucose (mg/dL)	< 180†	< 140

*An A1C of ≥ 7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level as close to the nondiabetic range as possible or, at a minimum, decreasing the A1C to 7%.

†If A1C remains above the desired target, postprandial levels, usually measured 90-120 minutes after a meal, may be checked. They should be < 180 mg/dL to achieve A1C levels in the target range.

Nathan DM, et al. Diabetes Care. 2006;29:1963-72.
American Association of Clinical Endocrinologists. Endocr Pract. 2007;13(suppl 1):3-68. Page 1-141

Recommended Glycemic Goals

- More Intensive Control
  - Those with a shorter duration of Diabetes
  - Long life expectancy
- Less Intensive Control
  - Those at greater risk of hypoglycemia
  - Longer Duration of Diabetes
  - Short life expectancy
- In frail, older adults
  - American Geriatrics Society
    - A1c < 8%
  - Veterans Affairs and Department of Defense
    - A1C 8-9%
  - American Diabetes Association
    - "less stringent glycemic goals"

Brown AF et al. J Am Geriatr Soc. 2003;51(Suppl):S265-S280.
American Diabetes Association. Diabetes Care. 2007;30(suppl 1):S4-S41.

A1C and Average Blood Glucose

A1C	Average Blood Glucose
6.0%	126 mg/dL
7.0%	154 mg/dL
8.0%	183 mg/dL
9.0%	212 mg/dL
10.0%	240 mg/dL
11.0%	269 mg/dL
12.0%	298 mg/dL

eAG = (28.7 X HbA1c) – 46.7

Nathan DM et al. Diabetes Care. 2006;29:1963-72.

THERAPY OF DIABETES MELLITUS

- D iet
- E xercise
- E ducation
- D rugs
- S elf-monitoring

Medical Nutrition Therapy for Diabetes

- Carbohydrates: 4 kcal/gram, 60-70% of daily calories
  - Sugars
  - Starch
  - Fiber
  - CHO's impact glucose levels the greatest
- Proteins: 4 kcal/gram, 15-20% of daily calories
  - Recommended 1g/kg for adults, 1.2g/kg for kids
- Fat: 9 kcal/gram, 10-20% of daily calories
  - Recommendations:
    - Saturated fat < 10%
    - Cholesterol <300mg
    - Trans minimal

ADA. Standards of Medical Care in Diabetes. Diabetes Care 2012;35(S1):S11-S63. Page 1-142

Physical Activity Recommendations

- At least 150 min/week of moderate intensity aerobic physical activity (50-70% of max heart beat) OR
- 90 min/week of vigorous aerobic activity (>70% of max heart beat)
  - Done at least three days a week without doing 2 consecutive days in a row
- Resistance exercise is recommended for type 2 patients three times weekly

ADA. Standards of Medical Care in Diabetes. Diabetes Care 2012;35(S1):S11-S63. Page 1-142

Diabetes Management

In The Old Days:
Simple but tasteless

TODAY:
A tantalizing array of choices …

Animal Insulins
Sulfonylureas

Biguanide
a-glucosidase inh
Insulin analogs
TZD
Meglitinides
Amylin analog
Incretin mimetics
DPP-4 Inhbitors
Resin Binder
Dopamine agonist

Treatment Options

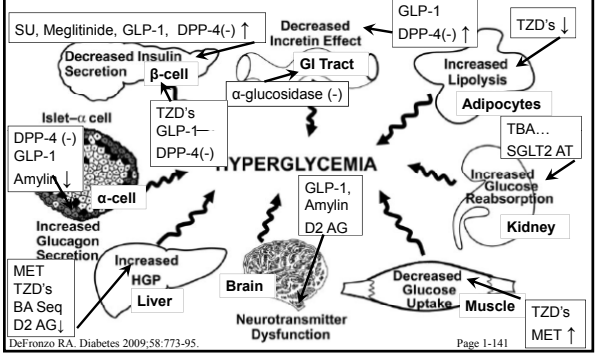
Oral Options

- Sulfonylureas
- Biguanide
- Alpha-Glucosidase Inhibitors
- TZD
- Meglitinides
- DPP-4 Inhibitors
- Resin Binder
- Dopamine Agonist

Parenteral Options

- Amylin Analogue
  Symlin (pramlintide)
- Incretin Mimetic Byetta (exenatide)
  Victoza (liraglutide)
- Insulin
  - Basal
  - Prandial
  - Mixed

Ominous Octet:
New Paradigm for treatment of T2DM



DeFronzo RA. Diabetes 2009;58:773-95. Page 1-141

Drug & Primary Glycemic Effect

Fasting	Mixed	PPG
Metformin	Sulfonylurea	Regular insulin
NPH insulin (HS)	TZD	Lispro/Aspart/ Glulisine insulins
Detemir insulin	Bile Acid Resin	Alpha-glucosidase
Glargine insulin	Liraglutide	Meglitinide
	Exenatide weekly	DPP-4 Inhibitors
		Bromocriptine
		Symlin
		Exenatide

Sulfonylureas
(Glimipizide, Glipizide, Glyburide)

- Mechanism of Action
  - Insulin secretagogue
- Efficacy
  - A1C lowering of 1-2% (The bigger they are…)
  - Mixed glucose effect (Fasting and PP)
  - 50% of max dose; 80% of effect
  - 5-10% primary failure rate; 5-10%/yr secondary
- Dose
  - Glimepiride 1-8 mg QD, glyburide 2.5 mg – 10 mg BID, glipizide up to 5-20 mg BID, 20 mg QD for XL
- Adverse Effects
  - Hypoglycemia (esp. glyburide in elderly)
  - Weight gain
  - Less common: Rash, photosensitivity, dyspepsia, nausea

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Sulfonylureas (Glimepiride, Glipizide, Glyburide)

- Contraindications
  - Hypoglycemic unawareness
  - Severe liver or kidney disease
- Advantages
  - Works quickly (within hours)
  - Effective
  - High initial response rate
  - Inexpensive
- Disadvantages
  - Hypoglycemia
  - Weight gain
  - Eventual treatment failure
  - Cardiovascular concerns?

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Metformin (Glucophage, Fortamet, Riomet, Glumetza)

- Mechanism of Action
  - Decrease hepatic glucose production
  - Secondarily some improvement of peripheral insulin resistance
  - May decrease intestinal absorption of glucose (small intestine)
- Efficacy
  - ADA recommended drug of choice
  - Hemoglobin A1c lowering of 1%–2%
  - Primarily reduces FPG
  - 5%–10% per year secondary failure rate
- Dose
  - 500 mg once or twice daily with food to start (decrease GI adverse effects); maximum of 2550 mg/day (1 gm BID)
- Adverse Effects
  - Common: GI - nausea, vomiting, diarrhea (especially early)
  - Uncommon: Macrocytic anemia (caused by vitamin B12 deficiency); lactic acidosis (uncommon but life threatening! Use only in appropriate patients)

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Metformin (Glucophage, Fortamet, Riomet, Glumetza)

- Contraindications
  - Serum creatinine of $\geq$ 1.5 mg/dL in men; $\geq$ 1.4 mg/dL or greater in women
  - Creatinine clearance less than 50 mL/minute?
  - Severe hepatic, pulmonary, or cardiac disease
  - Hold for 24 hours before and after procedures using contrast dye
- Advantages
  - Improved CV outcomes? (UK Prospective Diabetes Study obese patients)
  - No hypoglycemia as monotherapy
  - Weight neutral
  - High initial response rate
  - Positive lipid effects
  - Inexpensive
- Disadvantages
  - Patients eventually stop responding to therapy.
  - Gastrointestinal SE's especially early
  - Lactic Acidosis (in inappropriate candidates)

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Meglitinides (Repaglinide-Prandin, Nateglinide-Starlix)

- Mechanism of Action
  - Short-acting Insulin secretagogue
- Efficacy
  - Hemoglobin A1c reduction of 0.5%–1% (Repag > Nateg) as monotherapy or add-on therapy
  - A1c reductions of 1.5%–1.8% in combination with metformin or thiazolidine
  - Reduces postprandial blood glucose
  - Mealtime (e.g., 3 times/day) dosing may reduce adherence
- Dose
  - Repaglinide (Prandin): 0.5–1 mg 1–15 minutes before meals; mean daily dose 16 mg
  - Nateglinide (Starlix): 60-120 mg before meals
- Adverse Effects
  - Hypoglycemia (< sulfonylurea)
  - Modest weight gain (< sulfonylurea)

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Meglitinides (Repaglinide-Prandin,Nateglinide-Starlix)

- Contraindications
  - Hypoglycemic unawareness
  - Severe renal / hepatic impairment
  - Repaglinide together with gemfibrozil
- Advantages
  - Rapid onset of action
  - Less hypoglycemia and weight gain compared with sulfonylurea
  - Targets postprandial glucose
- Disadvantages
  - Hypoglycemia
  - Weight gain
  - Frequent dosing
  - Eventual treatment failure

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Alpha-glucosidase inhibitors (Acarbose-Precose, Miglitol-Glyset)

- Mechanism of Action
  - Inhibits the enzyme α-glucosidase, found along the brush border of the small intestine; responsible for the breakdown of complex carbohydrates into glucose, thus delaying and reducing post-meal carbohydrate absorption (and postprandial blood glucose)
- Efficacy
  - Hemoglobin A1c reduction of 0.5%–1%
  - Reduces postprandial blood glucose
  - Mealtime (e.g., 3 times/day) dosing (may reduce adherence)
- Dose
  - Acarbose (Precose): 25 mg with first bite of meal; start every day and then increase weekly to 2 times/day; then 3 times/day with meals to decrease GI adverse effects
  - Miglitol (Glyset): 25 mg with first bite of meal
- Adverse Effects
  - Common: Flatulence, abdominal discomfort, diarrhea; occur in up to 80% of patients but may diminish after 4–8 weeks of therapy
  - Rare: Liver function test (LFT) elevation

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Alpha-glucosidase inhibitors (Acarbose-Precose, Miglitol-Glyset)

- Contraindications
  - IBD - Ulcerative Colitis, Crohn's, bowel obstruction, Short bowel
  - Intestinal obstruction
  - Malabsorption
  - Creatinine clearance less than 25 mL/minute or serum creatinine greater than 2 mg/dL
  - Cirrhosis
- Advantages
  - No hypoglycemia as monotherapy (Note: Use only simple sugar [e.g., glucose, fructose, lactose] to treat hypoglycemia in patient receiving combination therapy, not sucrose.)
  - Weight neutral (adverse GI side effects may lead to some weight loss)
- Disadvantages
  - Modest efficacy
  - Poorly tolerated GI adverse effects
  - Frequent dosing

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Thiazolidinediones (Rosiglitazone-Avandia, Pioglitazone-Actos)

- Mechanism of Action
  - PPAR-gamma agonist
    - Increase peripheral muscle and adipose tissue insulin sensitivity
      - Decreases insulin resistance
    - Decrease hepatic glucose production

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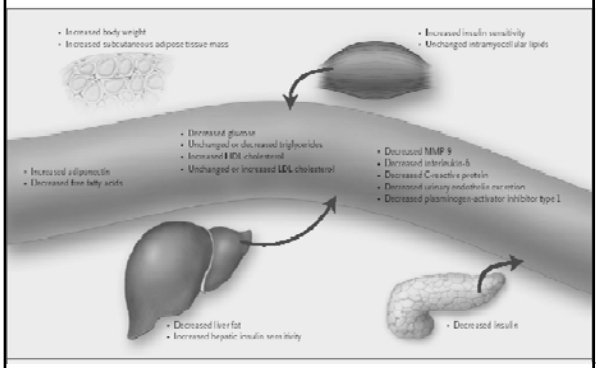
Thiazolidinediones: Mechanism of Action



Yki-Jarvinen H. N Engl J Med. 2004;351:1111.

TZD's (Rosiglitazone-Avandia, Pioglitazone-Actos)

- Efficacy
  - Hemoglobin A1c lowering of 0.8%–1.5%
  - Mixed blood glucose lowering effect
  - Long lag time before observe glycemic effect (weeks); maximal effect 8–12 weeks
  - Increases HDL-C (both) and lowers TG (pioglitazone)
- Dose
  - Pioglitazone (Actos): 15–45 mg/day
  - Rosiglitazone (Avandia): 1–2 mg/day, up to 8 mg/day (twice-daily is more effective) September 23, 2010: FDA restricted access program
- Adverse Effects
  - Weight gain
  - Fluid retention (especially with insulin, NSAID, GC, or DHP-CCB use)
  - Heart failure exacerbation
  - "Atypical" bone fractures (hands and feet)
  - Potential myocardial infarctions (rosiglitazone)
  - Bladder cancer
  - Rare hepatotoxicity

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TZD's (Rosiglitazone–Avandia, Pioglitazone–Actos)

- Contraindications
  - ALT > 2.5 ULN
  - NYHA Class III and IV HF
- Advantages
  - No hypoglycemia as monotherapy
  - Several favorable metabolic effects
  - Can use in renal insufficiency
  - Potential B-cell sparing effect?
  - Can induce ovulation in women with PCOS
- Disadvantages
  - Delayed onset of action
  - Adverse effects (weight gain, edema, fractures)
  - Periodic LFT monitoring recommended
  - Can induce ovulation in women with PCOS

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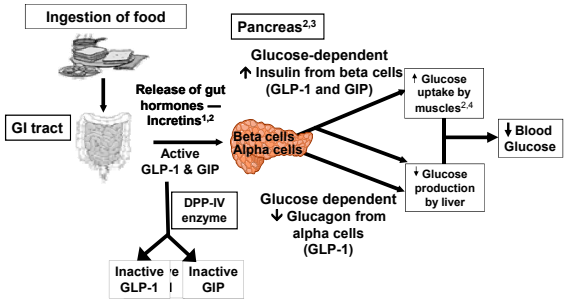
The Incretin Effect

- Insulin secretory response is greater to oral glucose than IV glucose
- Accounts for up to 60% of post-prandial insulin secretion in healthy individuals
- Attributed to hormones released from intestinal mucosal cells upon GI exposure to nutrients
  - GLP-1 (Glucagon-like peptide-1)
  - GIP (Glucose-dependent insulinotropic polypeptide)

Idris I and Donnelly R. Diabetes Obes Metab. 2007;9:153-65.

Role of Incretins in Glucose Homeostasis



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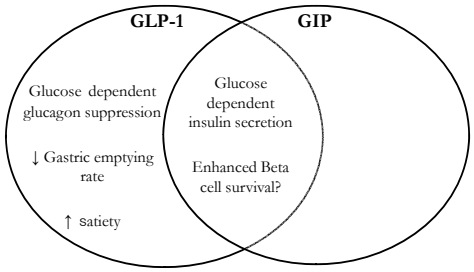
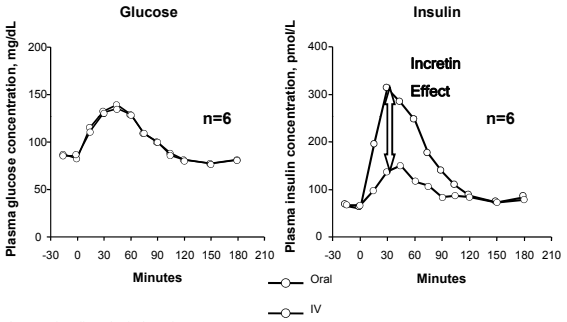
3. Drucker DJ. Diabetes Care. 2003;26:2929–40.
4. Holst JJ. Diabetes Metab Res Rev. 2002;18:430–41.

Incretins: GLP-1 and GIP



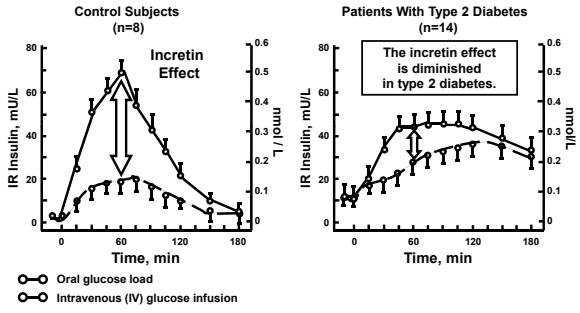
Drucker DJ et al. Lancet. 2006;368:1696-705.

The Incretin Effect: Greater Insulin Response After Oral vs IV Glucose in Healthy Individuals



Nauck MA et al. J Clin Endocrinol Metab. 1986;63:492-498.

The Incretin Effect in Subjects Without and With Type 2 Diabetes



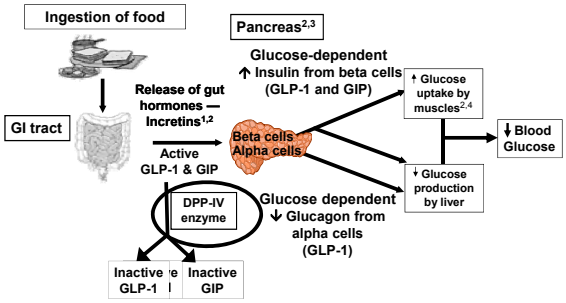
Adapted from Nauck M et al. *Diabetologia.* 1986;29:46–52. Copyright © 1986 Springer-Verlag.

Endogenous Incretin Limitations In DM

- Incretin response is impaired in T2DM
  - Decreased response to GIP
  - Decreased secretion of GLP-1
- GLP-1 therapy limited by short half-life
  - Rapidly degraded by DPP-4
  - Inhibition of inactivation? (Incretin Enhancers)
    - Sitagliptin, Saxagliptin, Linagliptin

Drucker DJ et al. Lancet. 2006;368:1696-705.

Role of Incretins in Glucose Homeostasis



1. Kieffer TJ, Habener JF. Endocr Rev. 1999;20:876–913.
2. Ahrén B. Curr Diab Rep. 2003;2:365–72.
3. Drucker DJ. Diabetes Care. 2003;26:2929–40.
4. Holst JJ. Diabetes Metab Res Rev. 2002;18:430–41.

DPP-IV Inhibitors: Mechanisms of Action

- Prolong $t_{1/2}$ of endogenous GLP-1 & GIP by inhibiting their inactivation by DPP-4
  - Increase GLP-1 levels 2-3x normal
- Target T2DM pancreatic defects
  - Increase glucose-dependent insulin secretion
  - Decrease inappropriate glucagon secretion
- No effect on gastric emptying, satiety, or weight
- May help preserve Beta-cell function

Drucker DJ et al. Lancet. 2006;368:1696-705.

Page 1-146

Dipeptidyl peptidase-4 inhibitors

Sitagliptin *(Januvia),* Saxagliptin *(Onglyza),* Linagliptin *(Tradjenta)*

- Mechanism of Action
  - Inhibits the enzyme DPP-4 from breaking down endogenous GLP-1 and GIP, resulting in 2-3X increased endogenous incretin levels. This results in
    - Glucose-dependent increase in insulin secretion
    - Glucose-dependent inhibition of glucagon secretion
- Efficacy
  - Hemoglobin A1c lowering of 0.6%–0.8%.
  - Primarily lowers postprandial glucose levels
- Dose
  - Sitagliptin: 100 mg/day (50 mg/day CrCl 30–49 mL/minute; 25 mg/day for CrCl < 30 mL/minute)
  - Saxagliptin: 5 mg/day (2.5 mg/day CrCl <50 mL/minute)
  - Linagliptin: 5 mg daily (no dose adjustment necessary)
- Adverse Effects
  - Placebo-like incidence of adverse effects (upper respiratory, headache, urinary tract infections)
  - Rare: Pancreatitis, skin reactions

Baetta R, Corsini A. Drugs. 2011;71:1441-67.

Page 1-146

Dipeptidyl peptidase-4 inhibitors

Sitagliptin(*Januvia*), Saxagliptin (*Onglyza*), Linagliptin (*Tradjenta*)

- Contraindications
  - History of pancreatitis
- Advantages
  - No hypoglycemia as monotherapy
  - Weight neutral
  - Placebo-like adverse effect profile
  - Potential B-cell sparing effect?
- Disadvantages
  - Modest A1c lowering
  - Expensive

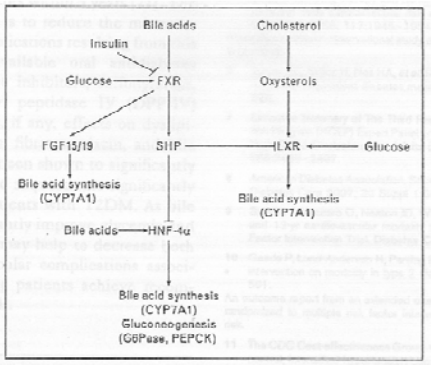
Page 1-146

Colesevelam - Welchol

- Mechanism of Action
  - Farnesoid X receptor (FXR) antagonist.
  - Bile acids activate the farnesoid X receptor (FXR), which leads to increased expression of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme necessary for hepatic gluconeogenesis. Colesevelam inhibits bile acid reabsorption, thus preventing FXR activation and upregulation of PEPCK, leading to decreased hepatic glucose production.

Page 1-146

Bile Acid and Glucose Metabolism



Goldfine AB. Curr Opin Cardiol. 2008;23:502-11.

Colesevelam Indications

Reduction of Elevated LDL-Cholesterol

Indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor

Reduction of Blood Glucose

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Welchol PI

Colesevelam - Welchol

- Mechanism of Action
  - Farnesoid X receptor (FXR) antagonist. Bile acids activate the farnesoid X receptor (FXR), which leads to increased expression of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme necessary for hepatic gluconeogenesis. Colesevelam inhibits bile acid reabsorption, thus preventing FXR activation and upregulation of PEPCK, leading to decreased hepatic glucose production.
- Efficacy
  - Hemoglobin A1c lowering of 0.4%–0.6%
  - Mixed blood glucose–lowering effect
  - LDL-C reduction of 15%–18%
- Dose
  - 625-mg tablets, 3 tablets twice daily or 6 tablets every day with meals
  - Suspension 3.75 g/packet, 1 every day with largest meal
- Adverse Effects
  - Constipation/dyspepsia
  - Potential TG increase (don't use if TG > 500 mg/dL)

Page 1-147

Colesevelam - Welchol

- Contraindications
  - Bowel obstruction
  - Triglycerides greater than 500 mg/dL
  - History of hypertriglyceridemia-induced pancreatitis
- Advantages
  - No hypoglycemia as monotherapy
  - Low-density lipoprotein cholesterol lowering of 15%–18%
- Disadvantages
  - Modest A1c efficacy
  - High pill burden
  - May raise TG
  - Potential for drug interactions (levothyroxine, ezetimibe, phenytoin)

Page 1-147

Bromocriptine - Cycloset

- Mechanism of Action
  - Dopamine receptor agonist
  - Glucose-lowering mechanism is unknown but improves glucose and energy metabolism and does NOT increase plasma insulin concentration; acts to reset aberrant central neurometabolic control of peripheral metabolism toward normal in patients with diabetes, resulting in a reduction in insulin resistance; improves glucose and energy metabolism through activation of central nervous system dopaminergic pathways responsible for metabolic control (Cycloset PI).
- Efficacy
  - Hemoglobin A1c lowering of 0.4%–0.6%
  - Mixed glucose effect (modest fasting and PPG)
- Dose
  - 0.8-mg tablet each morning (within 2 hours of waking) with food; titrate by 0.8 mg/week to mean daily dose of 4.8 mg (6 tablets) q AM
- Adverse Effects
  - Nausea/vomiting
  - Asthenia
  - Constipation
  - Dizziness
  - Somnolence

Page 1-147

Bromocriptine - Cycloset

- Contraindications
  - Hypersensitivity to ergot derivative or dopamine
  - Lactation (may inhibit)
  - Syncopal migraines
- Advantages
  - Unique mechanism of action
- Disadvantages
  - Modest efficacy
  - Adverse effects

Page 1-147

Combination Oral Diabetes Medications

- Actoplus Met—Pioglitazone and metformin
- Avandamet—Rosiglitazone and metformin
- Avandaryl—Rosiglitazone and glimepiride
- Duetact—Pioglitazone and glimepiride
- Glucovance—Glyburide and metformin
- Janumet—Sitagliptin and metformin
- Janumet XR—Sitagliptin and metformin XR
- Jentadueto—Linagliptin and metformin
- Kombiglyze XR—Saxagliptin and extended-release metformin
- Metaglip—Metformin and glipizide
- Prandimet—Repaglinide and metformin

Page 1-148

Advantages and Disadvantages of Fixed Drug Combinations

- <u>Advantages</u>
  - Convenience
  - Compliance
  - Efficacy
  - Dose Sparing
  - Single co-pay
- <u>Disadvantages</u>
  - Potential for multiple SE's
  - Dosing Inflexibility

Case #2

- A 65-year-old patient with type 2 DM, diagnosed 3 years ago, is currently treated with sitagliptin. He notes that his FBG is too high (180–200 mg/dL). He has a seafood allergy, no known drug allergies, and normal organ function. Which one of the following medication recommendations is best?

A. Acarbose
B. Bromocriptine
C. Metformin
D. Repaglinide

Workbook Page 1-148; Answer: Page 1-168.

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A. Acarbose
B. Bromocriptine
C. Metformin
D. Repaglinide

Workbook Page 1-148; Answer: Page 1-168.

Amylin Analog - Pramlintide (Symlin)

- Mechanism of Action
  - Synthetic analog of human amylin
    - Inhibits glucagon secretion in a glucose-dependent manner
    - Reduces the rate of gastric emptying
    - Increases satiety
- Efficacy
  - Hemoglobin A1c lowering of 0.5%–0.7%
  - Primarily lowers postprandial glucose levels
- Dose
  - Type 1 DM: Initiate at 15 mcg subcutaneously with meals daily, increase by 15 mcg per dose every 3–7 days based on tolerability and response; maximum of 60 mcg with meals
  - Type 2 DM: Initiate at 60 mcg with meals, increase to 120 mcg with meals in 3–7 days
- Adverse Effects
  - Nausea
  - Vomiting
  - Hypoglycemia with insulin (mealtime insulin doses must be reduced by 50% at drug initiation!)

Page 1-148

Pramlintide (Symlin)

- Contraindications
  - Gastroparesis
  - Hypoglycemic unawareness (Neuroglycopenia)
  - Hemoglobin A1c greater than 9%
  - Patients unwilling to self-monitor blood glucose
- Advantages
  - Use is associated with weight loss
- Disadvantages
  - Gastrointestinal adverse effects
  - Requires three additional injections per day (cannot be mixed with insulin)
  - Modest A1C reduction
  - May reduce the rate and extent of absorption of drugs that require rapid absorption (pain relievers, antibiotics, and oral contraceptives); separate administration by at least 1 hour

Page 1-149

Endogenous Incretin Limitations In DM

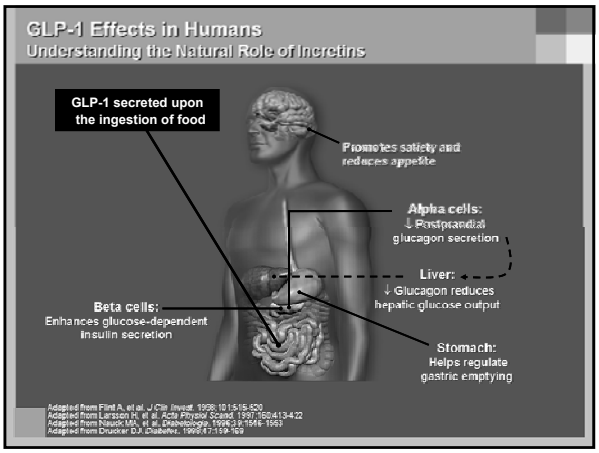
- Incretin response is impaired in T2DM
  - Decreased response to GIP
  - Decreased secretion of GLP-1
- GLP-1 therapy limited by short half-life
  - Rapidly degraded by DPP-4
  - Inhibition of inactivation? (Incretin Enhancers)
    - Sitagliptin, Saxagliptin, Linagliptin
  - Analogues resistant to DPP-4? (Incretin Mimetics)
    - Exenatide, Liraglutide

Drucker DJ et al. Lancet. 2006;368:1696-705.

Incretin Mimetics

- Mechanism of Action
  - Synthetic analog of human glucagon-like peptide-1, resistant to DPP-4, results in supraphysiologic (pharmacologic) incretin levels, causing
    - a glucose-dependent increase in insulin secretion
    - a glucose-dependent inhibition of glucagon secretion
    - reduced gastric emptying
    - increased satiety

Page 1-149



Incretin Mimetics

- Efficacy
  - Hemoglobin A1c lowering of 0.6%–1.5%
  - Primarily a postprandial glucose reduction with exenatide
  - Less postprandial and greater fasting glucose reduction with liraglutide and weekly exenatide
- Dose
  - Exenatide (Byetta): 5 mcg subcutaneously 2 times/day (thigh, abdomen, or upper arm) 1–60 minutes before morning and evening meals, increase to 10 mcg 2 times/ day after 4 weeks if tolerated
  - Liraglutide (Victoza): 0.6 mg subcutaneously every day (independent of meals; inject into thigh, abdomen, or upper arm); increase by weekly intervals to 1.2 mg subcutaneously every day; then 1.8 mg subcutaneously every day if needed
  - Exenatide LAR (Bydureon): 2 mg subcutaneously weekly (thigh, abdomen, or upper arm); two weeks before see effect
- Adverse Effects
  - GI: Nausea, Vomiting, Diarrhea
  - Headache
  - Rare: Pancreatitis/Renal dysfunction

Page 1-149

Incretin Mimetics

- **Contraindications**
  - Gastroparesis
  - Pancreatitis
  - Exenatide and Ex LAR: Creatinine clearance < 30 mL/minute
  - Liraglutide and Ex LAR: Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (MEN2)
- Advantages
  - Use is associated with weight loss (2-3 kg)
  - Convenient dosing
  - B-cell sparing effect?
- Disadvantages
  - Gastrointestinal adverse effects
  - Requires 1-2 injections per day
  - Modest A1C reduction
  - May reduce the rate and extent of absorption of drugs that require rapid absorption (pain relievers, antibiotics, and oral contraceptives); separate administration by at least 1 hour
  - Cost

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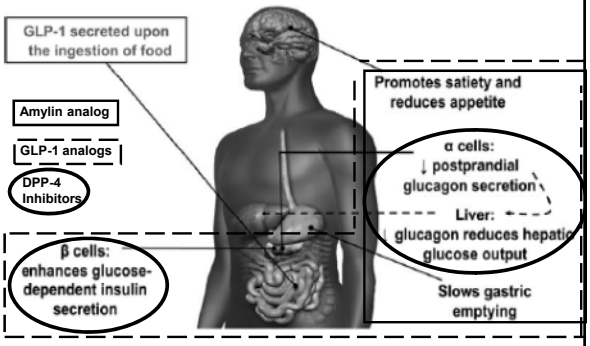
Incretin Comparison

	GLP-1 Activation	DPP-4 Inhibition
↑ Insulin	+++	+++
↓ Glucagon	+++	++
↓ Gastric emptying	+++	--
↑ Satiety	+++	--
Hypoglycemia	+/-	+/-
Nausea/Vomiting	+++	--
Weight	Loss	No Change
Route of admin	Injection	Oral
	e.g. exenatide, liraglutide	e.g. sitagliptin, saxagliptin, linagliptin

Effects of Amylin and Incretins



Idris I, Donnelly R. Diabetes Obes Metab. 2007;9:153-65.

Case #3

- A patient with type 2 DM receiving premeal insulin is interested in a "new" drug that he heard will allow him to significantly decrease his premeal insulin doses and allow better glycemic control. This drug is which one of the following?

☐ A. Liraglutide
☐ B. Metformin
☐ C. Pramlintide
☐ D. Bromocriptine

Workbook Page 1-150; Answer: Page 1-168.

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B. Metformin
C. Pramlintide
D. Bromocriptine

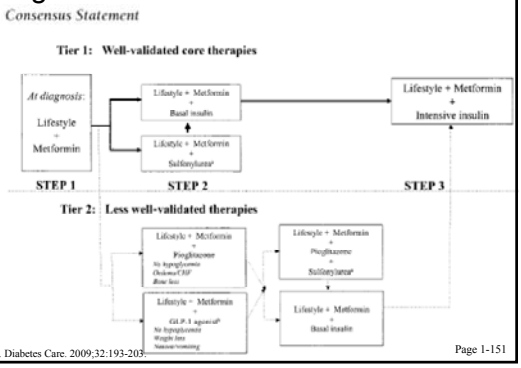
Workbook Page 1-150; Answer: Page 1-168.

Considerations for Initiation of Drug Therapy

- Baseline A1C/ Blood sugars
- Organ Function
- CI's to therapy
- Duration of DM
- SMBG
- Hypoglycemic Unawareness
- Baseline Weight
- Route of administration
- Start with single or combination drug therapy?
- Cost

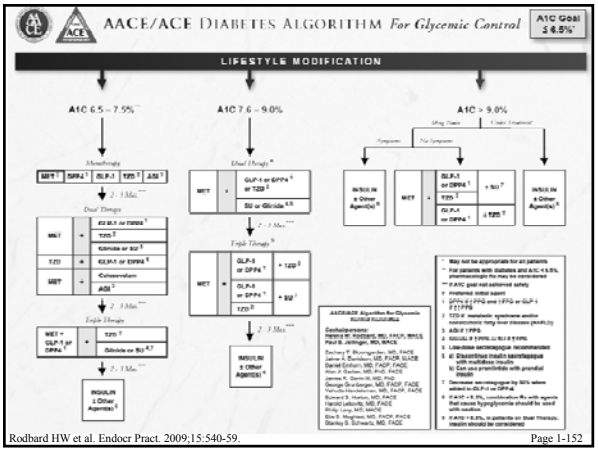
Page 1-150

ADA/EASD Consensus Algorithm Management of T2DM



Nathan DM et al. Diabetes Care. 2009;32:193-203.

Page 1-151



Rodbard HW et al. Endocr Pract. 2009;15:540-59.

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Ominous Octet vs. ADA

Pathogenesis of type 2 diabetes: implications for therapy

1) Effective treatment of type 2 diabetes requires multiple drugs used in combination to correct multiple pathophysiological defects.
2) Treatment should be based on known pathogenic abnormalities and not simply on reduction of A1C.
3) Therapy must be started early in the natural history of type 2 diabetes to prevent progressive β-cell failure.

DeFronzo RA. Diabetes 2009;58:773-795.

DEFRONZO ALGORITHM

Lifestyle + TRIPLE COMBINATION: TZD + Metformin + Exenatide

BAM!

HBA1c < 6.0%

	ADA	PATHOPHYSIOLOGIC-BASED
Durability	No	Yes
β Cell Preservation	No	Yes
Hypoglycemia	Yes	No
Weight Gain	Yes	No

DeFronzo RA. Diabetes. 2009;58:773-95.

Case #4

- J.L. is a 48-year-old obese white woman with type 2 DM, currently receiving metformin 1 g twice daily, whose postprandial blood glucose is higher than desired, and her most recent hemoglobin A1c is 7.5%. Which one of the following best represents how J.L.'s diabetes regimen should be changed?

A. Increase the metformin dose to 850 mg three times/day.
B. Substitute metformin with a sulfonylurea.
C. Add a bedtime dose of neutral protamine Hagedorn (NPH) insulin.
D. Add sitagliptin 100 mg orally every day.

Workbook Page 1-153; Answer: Page 1-168.

Case #4

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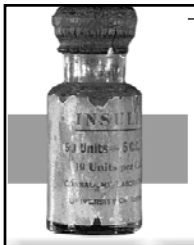
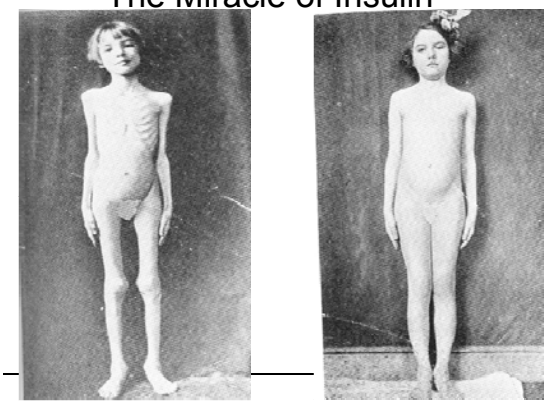
Workbook Page 1-153; Answer: Page 1-168.



The Discovery of INSULIN: 1921

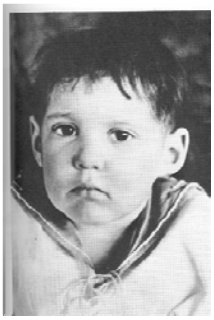
Sir Frederick Grant Banting | Charles Herbert Best | James Bertram Collip | John James Rikard Macleod

The Miracle of Insulin



1922: Before Insulin | 1923: After Insulin

JI: December 15, 1922.



JI: February 15, 1923.

Comparison of Human Insulins

Insulin	Onset	Peak	Duration
Lispro, Aspart, Glulisine	5-15 mins	1-2 hrs	3-5 hrs
Human Regular	30-60 mins	2-4 hrs	6-8 hrs
Human NPH	1-2 hrs	6-12 hrs	10-16 hrs
Insulin Detemir	3-4 hrs	Peakless	6-24 hrs
Insulin Glargine	4-6 hrs	Peakless	~24 hrs

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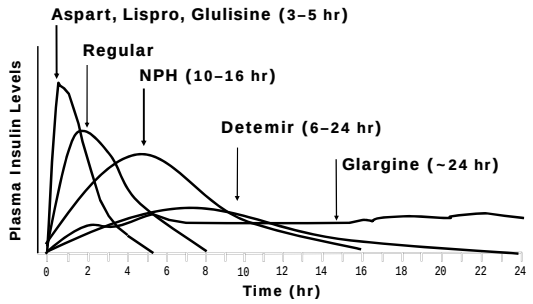
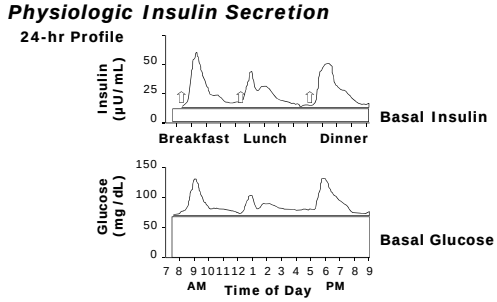
Insulin Profiles



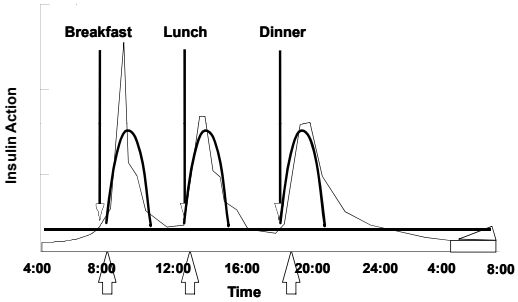
Rosenstock J. *Clin Cornerstone.* 2001;4:50.

Mimicking Nature With Insulin Therapy



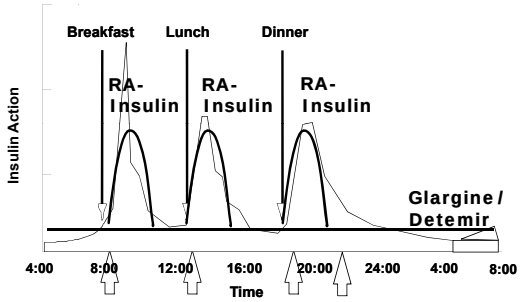
Skyler JS. In: DeFronzo RA, ed. *Current Therapy of Diabetes Mellitus.* St. Louis: Mosby-Year Book; 1998:108-116; Galloway JA, Chance RE. *Horm Metab Res.* 1994;26:591

Mimicking Nature: Basal-Bolus Insulin Concept



Adapted with permission from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy*. New York: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med.* 2002;347:1342

The Poor Man's Pump
Glargine/Detemir + Rapid-Acting Insulin



Adapted with permission from Leahy J. In: Leahy J, Cefalu W, eds. *Insulin Therapy*. New York: Marcel Dekker; 2002:87; Nathan DM. *N Engl J Med.* 2002;347:1342

The Concept of Basal/Bolus

- **Basal Insulin (detemir, glargine, NPH)**
  - Decreases fasting/preprandial glucose production
  - Requires consistent (constant) insulin levels
  - Approximates 50% of daily insulin needs
  - Equivalent doses
- **Bolus Insulin (regular, aspart, glulisine, lispro)**
  - Limits PPHG
  - Requires immediate insulin peak
  - Each meal requires 10-20% of daily insulin requirements

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Glucose Monitoring and Insulin Titration

Target Blood Glucose	Target Insulin
Fasting (Pre-breakfast)	Bedtime or pre-dinner NPH, detemir, glargine
Pre-lunch	Pre-breakfast regular, aspart, glulisine, lispro
Pre-dinner	Pre-breakfast NPH/pre-lunch regular, aspart, glulisine, lispro
Bedtime	Pre-dinner regular, aspart, glulisine, lispro

NPH = neutral protamine Hagedorn.

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Basal Insulin Therapy

Fix Fasting First

Initiating Basal Insulin Therapy

- Continue oral agent(s) at same dosage (may eventually reduce or DC - especially secretagogue therapy)
- Add single HS insulin dose (10-20 Units or 0.1-0.2 units/kg)
  - Glargine Insulin
  - Detemir insulin
  - NPH insulin
- Adjust insulin dose according to Fasting Blood Sugars
- Adjust the insulin dose every 3-4 days as needed
  - Increase 2 U if FBG 100–120 mg/dL
  - Increase 4 U if FBG 121–140 mg/dL
  - Increase 6 U if FBG 141–180 mg/dL
  - Increase 8 U if FBG >180 mg/dL
- Reduce dose immediately if experience fasting hypoglycemia.
- Treat to target (usually FPG 80–100 mg/dL)

Page 1-154

Initiation and Adjustment of Insulin in T2DM

Nathan DM et al. Diabetes Care. 2009;32:193-203.

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Case 5

- C.D. is a 19-year-old white woman, just given a diagnosis of type 1 DM. She weighs 80 kg and has normal renal function (serum creatinine 0.6 mg/dL). Which one of the following is the most appropriate empiric basal insulin and dose?

A. Aspart 20 units at bedtime.
B. Glargine 20 units at bedtime.
C. Regular insulin 40 units at bedtime.
D. NPH 40 units at bedtime.

Workbook Page 1-156; Answer: Page 1-168.

Case 5

- C.D. is a 19-year-old white woman, just given a diagnosis of type 1 DM. She weighs 80 kg and has normal renal function (serum creatinine 0.6 mg/dL). Which one of the following is the most appropriate empiric basal insulin and dose?

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B. Glargine 20 units at bedtime.
C. Regular insulin 40 units at bedtime.
D. NPH 40 units at bedtime.

Workbook Page 1-156; Answer: Page 1-168.

Initiating MDI Therapy

- Empiric Dosing - Insulin Analogues
  - Type 1 0.5 units/kg/d
  - Type 2 0.7-1.0 units/kg/d (obesity, activities)
  - Calculate Daily Dose
- Give 50% as Basal Insulin
- Give 50% as Bolus Insulin
  - Split into three doses
- Adjust accordingly:
  - Algorithm (The Rule of 1800)
  - Carbohydrate Counting

Page 1-156

Correctional Insulin Dosing

- Rule of 1800 (Rapid acting insulin)
  - 1800/current daily insulin dose equals the mg/dl change of glucose per 1 unit insulin
  - Titrate dose using algorithm
  - Example: Patient from last example
    - 40 units insulin/day 1800/40= 45 mg/dl per unit

Blood Glucose	
< 80	Subtract 1 unit from usual premeal insulin dose
80-125	Use usual premeal dose
126-170	Add 1 unit to usual premeal dose
171-215	Add 2 units to usual premeal dose
216-260	Add 3 units to usual premeal insulin dose

Page 1-156

Correctional Insulin Dosing

- Rule of 1500 (Regular insulin)
  - (1500/current daily insulin dose) equals mg/dl change of glucose per 1 unit insulin
  - Titrate dose using algorithm
  - Example:
    - 50 units insulin/day 1500/50= 30 mg/dl per unit

Blood Glucose	
< 80	Subtract 1 unit from usual premeal insulin dose
80-110	Use usual premeal dose
111-140	Add 1 unit to usual premeal dose
141-170	Add 2 units to usual premeal dose
171-200	Add 3 units to usual premeal insulin dose

Page 1-156

Insulin to Carbohydrate Ratio

- Rule of 500
  - (500/total current daily insulin dose) equals the insulin/carbohydrate ratio
  - Titrate dose using algorithm
  - Example:
    - 50 units insulin/day 500/50 = 10
    - Insulin/carbohydrate ratio equals 1 unit of insulin for every 10 grams of CHO ingested

Page 1-156

Case #6

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.
- 6. Which one of the following is Bill's insulin sensitivity?
  - A. 5 mg/dL
  - B. 10 mg/dL
  - C. 15 mg/dL
  - D. 18 mg/dL

Workbook Page 1-157; Answer: Page 1-168.

Case #6

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.
- 6. Which one of the following is Bill's insulin sensitivity?
  - A. 5 mg/dL
  - B. 10 mg/dL
  - C. 15 mg/dL
  - D. 18 mg/dL

Workbook Page 1-157; Answer: Page 1-168.

Case #7

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.
- 7. Which of the following is Bill's insulin/carb ratio?
  - A. 5
  - B. 10
  - C. 15
  - D. 18

Workbook Page 1-157; Answer: Page 1-168.

Case #7

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.
- 7. Which of the following is Bill's insulin/carb ratio?
  - A. 5
  - B. 10
  - C. 15
  - D. 18

Workbook Page 1-157; Answer: Page 1-168.

Case #8

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.
- 8. Bill's presupper reading today is 184 mg/dL (goal of 130 mg/dL), and he plans to eat 60 carbohydrates at dinner. Which one of the following represents what his pre-dinner lispro insulin dose should be?
  - A. 5
  - B. 10
  - C. 15
  - D. 18

Workbook Page 1-157; Answer: Page 1-168.

Case #8

- B.L. is a 70-year-old patient with type 2 DM, diagnosed 28 years ago. His indirect measure of endogenous insulin secretion (C-peptide level) is undetectable, and he receives a basal/bolus insulin regimen of glargine and lispro insulins. His insulin requirements total 100 units of insulin per day.
- 8. Bill's presupper reading today is 184 mg/dL (goal of 130 mg/dL), and he plans to eat 60 carbohydrates at dinner. Which one of the following represents what his pre-dinner lispro insulin dose should be?
  - A. 5
  - B. 10
  - C. 15
  - D. 18

Workbook Page 1-157; Answer: Page 1-168.

Mixed Insulins

- Humulin 70/30
  - 70% NPH, 30% Regular
- Novolin 70/30
  - 70% NPH, 30% Regular
- Humalog Mix 75/25
  - 75% lispro protamine, 25% lispro
- Humalog Mix 50/50
  - 50% lispro protamine, 50% lispro
- Novolog Mix 70/30
  - 70% aspart protamine, 30% aspart

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New Drug Treatment Requirements

- Approval of all new diabetes drugs is now contingent on proof of CV safety. New FDA regulations went into effect in 2008 in the wake of the rosiglitazone CV safety issues. The regulations require:
  - Approval of diabetes drugs only with the exclusion of a 30% relative increase in CV events compared with placebo or an active comparator, or of an 80% relative excess of events with a postmarketing study to formally evaluate the risk.
  - Data on patients with advanced diabetes, elderly patients, and those with some degree of renal impairment in the regulatory submission (groups typically excluded from pivotal trials).
  - At least 2 years of CV safety data, to include major adverse CV events as an end point with independent adjudication of events.

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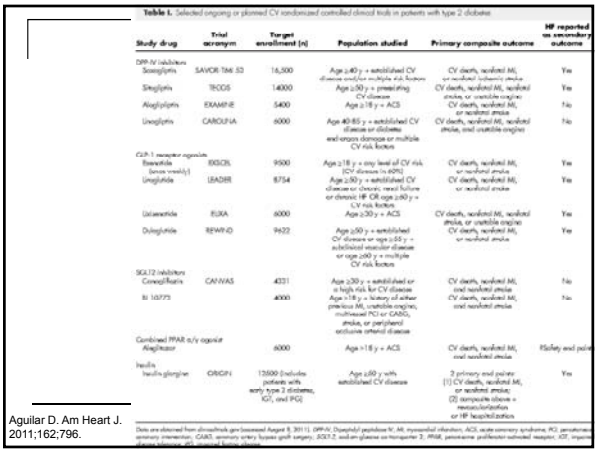
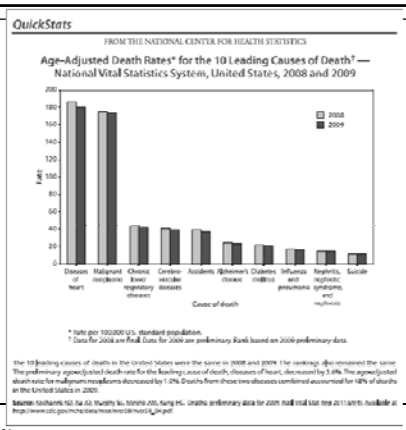


Aguilar D. Am Heart J. 2011;162:796.

The Cost of Diabetes – Per 24 Hours

(105 Million Americans with Diabetes or Pre-Diabetes)

- 4900 New Diagnoses of Diabetes
- 810 Deaths
- 230 Amputations
- 120 Cases of Kidney Failure
- 55 People Going Blind



MMWR. 2011;60:1656.

Diabetes Complications
Acute complications

- Hypoglycemia: Signs/symptoms of hypoglycemia (CNS/SNS)
  - Blood glucose usually below normal (less than 60 mg/dL)
  - Patient may:
    - Feel tremulous
    - Feel nervous/anxious
    - Be diaphoretic
    - Be tachycardic
    - Feel hungry
    - Experience a headache
  - Provider/family member may notice:
    - Irritability
    - Confusion
    - Sleepiness
- Diabetic Ketoacidosis
- Hyperglycemic hyperosmolar state

Page 1-158

Sick Day Rules for Insulin-treated Pts

- DO NOT STOP INSULIN !
- Keep usual basal insulin
- Cover with quick-acting insulin
- Frequent finger stick monitoring (q 1-2 hrs)
- Check urine ketones
- Use sport drinks to maintain hydration
- Supplement calories to support insulin coverage (glucose affected prior to ketones)
- If vomit, go to ER

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Diabetes Complications
Chronic complications

- Microvascular
  - Retinopathy
  - Nephropathy
- Macrovascular
  - Coronary artery disease
  - Cerebrovascular disease
  - Peripheral arterial disease
- Neurologic
  - Peripheral Neuropthy
  - Autonomic Neuropathy
    - Gastroparesis
    - Erectile dysfunction
    - Urinary retention
    - Diabetic diarrhea
    - Cardiovascular autonomic neuropathy (e.g., orthostatic hypotension, resting tachycardia)
    - Hypoglycemic unawareness (neuroglycopenia)

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The ABC's of Diabetes

- A1C (and ASA)
  - < 7.0% (ACE < 6.5%)
- Blood Pressure
  - < 130/80 mmHg (125/75 mmHg)
- Cholesterol (and Cessation of smoking)
  - LDL-C < 100 mg/dL (<70 mg/dL?)
  - Non-HDL-C < 130 mg/dL (<100 mg/dL?)
  - HDL-C > 40 mg/dL (> 50 mg/dL in women)
  - TG's < 150 mg/dL

Page 1-160

Recommendations for Primary Prevention of CVD in People With Diabetes

- Lifestyle Management
  - Weight Control
    - Weight reduction in obese individuals will reduce all the CVD risk factors associated with type 2 DM and will improve hyperglycemia.
    - Moderate weight loss versus ideal body weight
    - A 5%–10% weight loss is associated with profound health benefits.
    - Weight maintenance versus weight gain
    - Diet versus surgery
  - Medical Nutrition Therapy
    - Total energy intake to achieve body-weight goals
    - Total dietary fat intake: 25%–35% of total calories; mainly monounsaturated or polyunsaturated fat
    - Ample intake of dietary fiber (14 g/1000 calories)
    - Alcohol limited: 1 drink for women, 2 drinks/day for men
    - Lipid goal attainment
    - Saturated fats: 7% of energy intake
    - Dietary cholesterol intake: 200 mg/day
    - Intake of *trans*-unsaturated fatty acids: 1% of energy intake
    - Blood pressure attainment—A reduction in sodium intake: 1200–2300 mg/day
  - Physical activity
    - At least 150 minutes of moderate-intensity aerobic physical activity or 90 minutes of vigorous aerobic exercise per week
    - The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity
    - For long-term maintenance of major weight loss, a larger amount of exercise (7 hours of moderate or vigorous aerobic physical activity per week) may be helpful.

AHA and ADA. Circulation; 2007;115:114-26. Page 1-160

Recommendations for Primary Prevention of CVD in People With Diabetes

- Blood Pressure
  - Measure at every vist
  - BP Goal ≤ 130/80 mmHg
  - ACEI or ARB consideration
  - Combination therapy typically required
- Lipids
  - Measure at least annually
  - LDL-C goal of ≤ 100 mg/dL (or 30-40% reduction)
  - Non-HDL-C goal of ≤ 130 mg/dL
  - TG Goal of ≤ 150 mg/dL
  - HDL-C Goal ≥ 40 mg/dL in men, ≥ 50 mg/dL in women

AHA and ADA. Circulation; 2007;115:114-26. Page 1-160

Recommendations for Primary Prevention of CVD in People With Diabetes

- Tobacco
  - Ask each diabetes patient about tobacco use status at every visit.
  - Advise every tobacco user to quit.
  - Assess tobacco user's willingness to quit.
  - Assist patients willing to quit with counseling and by developing a plan to quit.
  - Follow-up, referral to special programs, or pharmacotherapy (e.g., nicotine replacement, bupropion) should be incorporated as needed.
- Antiplatelet
  - Aspirin therapy (75–162 mg/day) recommended in diabetes patients with increased CV risk (10-year risk of 10% or greater)
    - Men 50 years old with one additional risk factor
    - Women 60 years old with one additional risk factor (family history of CVD, HTN, smoking, dyslipidemia, or albuminuria).
  - CI's to ASA: ASA allergy, bleeding tendency, existing anticoagulant therapy, recent GI bleeding, clinically active hepatic disease.
  - Other antiplatelet agents may be a reasonable alternative for patients with high risk.
  - Do not recommend Aspirin therapy for patients younger than 21 years (risk of Reye syndrome).

AHA and ADA. Circulation; 2007;115:114-26. Page 1-161

Recommendations for Primary Prevention of CVD in People With Diabetes

▪ Lifestyle Management ▫ Weight Control Nutrition Therapy ▫ Physical activity	See Nutritionist, CDE, Dietician, or Exercise Medical Physiologist	
▪ Blood Pressure	Add ACEI/ARB	(2)
▪ Lipids	Fasting lipid profile, add statin	(4)
▪ Tobacco	Stop smoking – refer	(1)
▪ Antiplatelet Agents	Start daily ASA	(3)
▪ Glycemic Control	Your pick	(5)

AHA and ADA. Circulation; 2007;115:114-26.

My Diabetes Check-List

- Epidemiologic and interventional evidence define these interventions/targets
  - HbA_{1c} ≤7% (6%?) (Metabolically friendly)
  - Blood Pressure ≤130/80 mm Hg (ACEI/ARB)
  - LDL-cholesterol ≤70 mg/dL (Statin)
  - Daily ASA use for vascular protection
  - Smoking Cessation
  - Immunizations (Influenza, Pneumococcus)
  - Urinalysis
  - Daily Feet Inspection
  - Annual Dilated Eye Exams
  - Realistic Exercise Program
  - Weight Loss (5-10%)
  - Dental Exams (Peridontal Disease)

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Questions?

American College of Clinical Pharmacy

Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Endocrine Disorders

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Learning Objectives

- Identify the most vulnerable patient populations receiving thyroid hormone replacement, understanding the importance of consistent levothyroxine replacement.
- Review the pharmacotherapy of Graves disease, including the advantages and disadvantages of antithyroid drugs versus radioactive iodine and surgery.
- Recommend appropriate patient-specific pharmacotherapy for the treatment of polycystic ovary syndrome.
- Recognize the clinical presentation and treatment of a patient with adrenal insufficiency.
- Medically manage a patient presenting with hyperprolactinemia.
- Compare and contrast the available weight-loss medications with respect to efficacy and adverse effects, and design a patient-specific treatment plan for a patient who wishes to lose weight.

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Learning Objectives

- Compare and contrast the role of drug therapy, transsphenoidal surgery, and radiation therapy for a patient with a diagnosis of acromegaly, and design a patient-specific pharmacologic treatment/monitoring plan.
- Describe the typical clinical features of patients with growth hormone deficiency, and design an appropriate pharmacologic treatment and monitoring plan based on patient-specific factors.
- Identify indications when patients with Cushing syndrome would be candidates for pharmacologic treatment.
- List symptoms of hyperaldosteronism and recommend appropriate drug therapy for its treatment.
- List appropriate monitoring parameters for a patient with testosterone deficiency receiving testosterone replacement therapy.

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Endocrine Disorders

- Thyroid Disease
- PCOS
- Pituitary Disease
  - Prolactinomas
  - Growth Hormone Excess and Deficiency
- Obesity
- Adrenal Disease
  - Addison's Disease
  - Cushing's Syndrome
  - Hyperaldosteronism
- Male Hypogonadism

Thyroid Disease - Clinical Pearls

- HoTR: the great masquerader
- For primary thyroid disease, any test result (with one exception) below normal is consistent with HoTR, whereas any test result (with one exception) above normal is consistent with HTR; the one exception is TSH.
- TSH is the best test for screening patients for thyroid disease.
- The typical T4 replacement dose is about 1.6 mcg/kg
- T4 requirements increase by 40%–50% during pregnancy
- Although 5%–10% of postpartum women develop thyroiditis during the 12 months post-pregnancy, postpartum thyroiditis occurs in 25% of women with T1DM
- 10% of cold thyroid nodules are malignant.
- Every patient who gets a prescription for a thioamide should also receive a prescription for a complete blood cell count.

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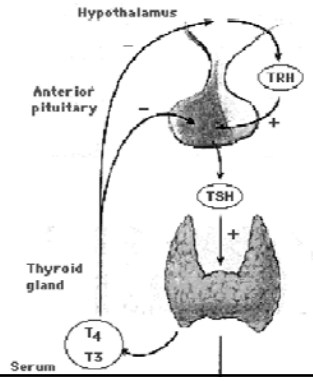
Thyroid Hormone Regulation



Page 1-173

HoTR - Causes

- Iatrogenic causes (surgical management or RAI for HTR, external radiation)
- Autoimmune (Hashimoto's thyroiditis)
- Medications (lithium, interferon)
- Cretinism
- Iodide deficiency
- Postpartum thyroiditis
- Post-inflammatory thyroiditis
- Secondary causes (pituitary or hypothalamic disease)

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Drug-induced Thyroid Disease

- Iodine-containing contrast dyes
- Amiodarone
- Iodinated Glycerol
- Lithium
- Alpha-Interferon
- Anti-thyroid Drugs
- Thyroid Hormone

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HoTR – Clinical Presentation

- Extreme fatigue
- Weight gain
- Depression
- Cold intolerance
- Dry skin/loss of hair
- Constipation
- Irregular, heavy menses
- Decreased concentration, forgetfulness
- Bradycardia
- Hypothermia
- Hoarseness
- Hyperlipidemia

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HoTR - Diagnosis

- Physical examination
  - Blood pressure and heart rate
  - Thyroid palpation and auscultation
- Laboratory evaluation
  - High TSH (in primary disease; TSH is low or low-normal in secondary disease); levels greater than 5 mIU/mL with symptoms or 10 mIU/mL without are typically treated (normal 0.4–4 mIU/L)
  - Low TT4 (normal 5–12 mcg/dL)
  - Low FT4 (normal 0.7–1.9 ng/dL)
  - Low TT3 (normal 80–180 ng/dL)
  - Thyroid autoantibodies (antithyroid peroxidase and antithyroglobulin autoantibodies) are present in most patients with Hashimoto.
  - Low RAI uptake (RAIU)—Normals are 3%–16% at 6 hours and 8%–25% at 24 hours; 131I
  - Thyroid scan (123I or 99mTc)

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HoTR - Screening

- The U.S. Preventive Services Task Force, 2004, found insufficient evidence to recommend for or against routine screening for thyroid disease in adults.
- The American Thyroid Association currently recommends that everyone older than 35 years be screened with a TSH test every 5 years.
- The American Association of Clinical Endocrinologists recommends that all women be tested for HoTR (by TSH level) by 50 years of age (sooner if they have a family history of thyroid disease) as well as those who are or planning to become pregnant.
- Thyroid ultrasound—Sound waves that image the thyroid gland; typically done when thyroid nodule is detected on physical examination
- Thyroid fine-needle aspiration—Biopsy of nodule to determine whether benign or malignant: firm, irregular, and fixed nodules; cold nodules as identified by thyroid uptake scan; presence of cervical lymphadenopathy; and patients with history of external neck irradiation during childhood have greater likelihood of malignancy

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HoTR - Treatment

- Levothyroxine (use a high-quality brand preparation: Levothroid, Levoxyl, Synthroid, Unithroid)—Treatment of choice
  - Rationale for use
    - Stable, pure, and predictable potency
    - Serum T3 concentration controlled physiologically
    - Long half-life, allows daily dosing
    - Twelve dosages available
    - Drug of choice—American Thyroid Association/American Association of Clinical Endocrinologists
    - Different products may not be therapeutically equivalent.
  - Mean replacement dosage of 1.6 mcg/kg of body weight per day; typically recommended to take on empty stomach

Page 1-174

HoTR - Treatment

- Levothyroxine Dosing
  - Appropriate pace of replacement depends on
    - Duration of the HoTR
    - Severity of the HoTR
    - Presence of other, associated medical disorders
  - Use initial doses of 12.5 mcg to full replacement dose.
  - Titrate dose to normalization of TSH level (primary disease); check TSH 6–8 weeks after each dose change, every 3–6 months during first year of diagnosis, and annually thereafter.

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HoTR – At Risk Populations Need for Consistent T4 Dosing

- Pregnant women
  - Treat even mildly elevated TSH (e.g., more than 3 mIU/L).
  - Increase T4 replacement by 30% with first detection of pregnancy.
  - Monitor TSH monthly and adjust dose accordingly (goal 1–2 mIU/L).
  - Suggestion for routine screening (see above under Screening)
  - Typically, a 40%–50% dose increase is required during pregnancy.
  - An appropriate maternal replacement dose poses no threat to the fetus; maternal HoTR increases risk of miscarriage and decreased IQ of offspring.
- Infants (congenital HoTR): Replace T4 with dose of 10–15 mcg/kg; can crush and mix with formula or breast milk; monitor with FT4 levels for first 6 months of life and then TSH thereafter
- Patients with thyroid cancer (papillary and follicular cancers): Use higher T4 doses for target TSH of 0.1–0.2 mIU/L.
- Patients with preexisting cardiac disease: Start low (12.5 mcg) and go slow (12.5-mcg increments every 6–8 weeks).
- Patients with preexisting osteopenia/osteoporosis
- Older people: Start low (12.5 mcg) and go slow (12.5-mcg increments every 6–8 weeks).

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T4 – Drug Interactions

- Decrease in T4 absorption; take T4 2 hours before or 6 hours after
  - Cholestyramine
  - Calcium
  - Ferrous sulfate
  - Sucralfate
  - Aluminum hydroxide
- Increase in T4 metabolism
  - Rifampin
  - Phenytoin
  - Phenobarbital
  - Sertraline
- Pharmacodynamic interactions
  - Warfarin
  - Digoxin

Page 1-175

Non-preferred Thyroid Hormone Products

- **Desiccated thyroid hormone (Thyroid USP)**
  - Variable amount of iodine
  - Variable ratio of thyroid hormones
  - Potential of allergic reactions
  - Potential of thyrotoxicosis
  - Variable potency among brands
  - 1 grain (65 mg) equivalent to about 60 mcg of T4
- **Triiodothyronine (Cytomel, Triostat)**
  - Stable, pure, and predictable potency
  - Greater potential for cardiac effects
  - Short half-life requires multiple daily dosing.
  - Need to monitor T3 levels
  - May be advantageous for myxedema coma
  - 25 mcg equivalent to about 60 mcg of T4
- **Synthetic T4/T3 combination (Liotrix—Thyrolar)**
  - Stable, pure, and predictable potency
  - Combination of synthetic T4 and T3 in a physiologic ratio of 4:1
  - Lack of therapeutic rationale
  - Disadvantages of T3 preparations (potential of thyrotoxicosis)
  - 1 grain (65 mg) equivalent to about 60 mcg of T4

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Patient Case #1

Ms. G. is a 44-year-old, 50-kg white woman with recently diagnosed Hashimoto's thyroiditis. She experiences weight gain, constipation, cold intolerance, and extreme fatigue. Her medical history is significant for hyperlipidemia and HTN. Her current medications include atorvastatin 10 mg once daily, HCTZ 25 mg once daily, and calcium carbonate 500 mg 2 times/day. Which one of the following is the most appropriate thyroid hormone replacement therapy for this patient?

- A. Synthroid 50 mcg once daily
- B. Cytomel 50 mcg 3 times daily
- C. PTU 100 mg 3 times daily
- D. Levothroid 150 mcg once daily

Workbook Page 1-176; Answer: Page 1-214

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- A. Synthroid 50 mcg once daily
- B. Cytomel 50 mcg 3 times daily
- C. PTU 100 mg 3 times daily
- D. Levothroid 150 mcg once daily

Workbook Page 1-176; Answer: Page 1-214

HTR - Causes

- Toxic diffuse goiter (Graves' disease)
- Toxic adenoma
- Toxic multinodular goiter (Plummer disease)
- Painful subacute thyroiditis
- Silent thyroiditis, including lymphocytic and postpartum variations
- Iodine induced HTR (Jod-Basedow)
- Excessive ingestion of thyroid hormone (factitious)
- Drugs (amiodarone)
- Tumor (excessive pituitary TSH or trophoblastic disease)

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HTR – Clinical Presentation

- Heat intolerance or increased sweating
- Tremor
- Palpitations and tachycardia
- Nervousness and irritability
- Frequent bowel movements or diarrhea
- Less frequent, shorter, and lighter menses
- Fatigue and muscle weakness
- Thyroid enlargement
- Weight loss despite an increased appetite
- Exophthalmos and/or pretibial myxedema (in Graves' disease)
- Insomnia

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HTR - Diagnosis

- Physical examination
  - Blood pressure and heart rate
  - Thyroid palpation and auscultation (to determine thyroid size, nodularity, and vascularity)
  - Neuromuscular examination
  - Eye examination (detect evidence of exophthalmos/ophthalmopathy)
  - Dermatologic examination
  - Cardiovascular examination
  - Lymphatic examination (nodes and spleen)
- Laboratory evaluation
  - Low TSH (in primary disease; TSH is high in secondary disease)
  - High TT4
  - High FT4
  - High TT3
  - Thyroid autoantibodies (TSH receptor antibody [TRAb], thyroid-stimulating immunoglobulin [TSI])
  - High RAIU
  - Thyroid scan (^{123}I or ^{99}mTc)

Page 1-177

HTR - Treatment

- Radioactive iodine (^{131}I)
  - Most common treatment of HTR
  - Contraindication in pregnancy and in nursing mothers
  - Very high risk of subsequent HoTR
- Surgery
  - TOC for thyroid cancer, respiratory or swallowing difficulties
  - Find an experienced surgeon!
  - Hypothyroidism
- Drug Therapy

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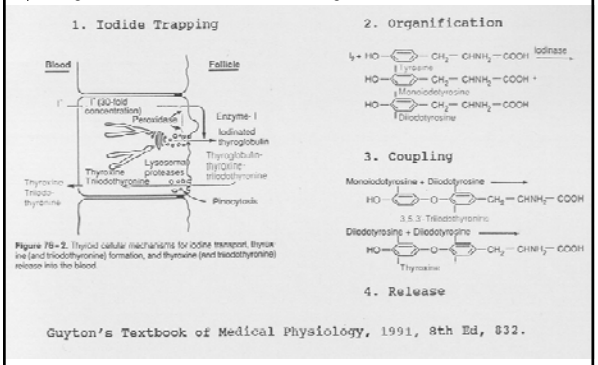
Thyroid Hormone Synthesis



Guyton's Textbook of Medical Physiology, 1991, 8th Ed, 832.

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HTR – Treatment
Thioamides

- Mechanism of action
  - Inhibits organification and coupling; PTU also inhibits the conversion of T4 to T3
  - Delayed effect (weeks)
- Dose
  - PTU: 300–600 mg/day in two or three divided doses; preferred in pregnancy (first trimester), lactation and thyroid storm)
  - Methimazole (Tapazole): 30–60 mg/day in one or two divided doses; longer half-life, better adherence, LESS HEPATOTOXICITY; recommended thioamide unless first trimester of pregnancy
  - Often used before RAI therapy or surgery; may use for 18–24 months in Graves disease in attempt at disease remission
- Adverse effects
  - Benign: Rash, fever, arthralgias
  - Severe: Agranulocytosis, hepatitis
- Patient information
  - Report fever, sore throat, flulike symptoms, abdominal pain, dark urine, or lightly colored stool.
  - When getting a prescription for thioamide, be sure to get one for a complete blood cell count.

Page 1-178

HTR – Treatment
Iodides

- **Mechanism of action**
  - Block thyroid hormone release
  - Inhibit organification
  - Inhibit the peripheral conversion of T4 to T3
  - Decrease gland size/vascularity
  - Rapid onset (days)
- **Dose**
  - Saturated solution of potassium iodide (38 mg/drop): 1–5 drops in juice 3 times/day
  - Lugol's solution (6 mg/drop): 3–5 drops in juice 3 times/day
  - Radiographic iodinated contrast agents: 1 g orally daily (Telepaque/Oragrafin/Hypaque)
  - Most commonly used in patients with Graves' disease before surgery, and in thyroid storm
- **Adverse effects**
  - Allergic reactions
  - Dose-related toxicity (iodism)
  - Metallic taste
  - "Escape" phenomenon
- **Contraindications**
  - Pregnancy
  - Prior to RAI therapy
  - Patients with nodular goiter or adenomas

Page 1-179

HTR – Treatment
Beta Blockers

- Mechanism of action
  - Manage sympathetic-mediated symptoms.
  - Inhibit peripheral T4 conversion (propranolol, nadolol).
  - Very quick onset of effect (hours)
- Dose
  - Propranolol 120–160 mg/day in three or four divided doses; maximum 640 mg/day
  - Nadolol 80 mg/day in one or two divided doses; maximum 320 mg/day
  - Used until more specific antithyroid therapy takes effect
- Adverse effects
  - Hypotension
  - Bradycardia
  - Fatigue

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Pharmacists' Role in
Patient Care and Monitoring

- Convey to patients the importance of adherence.
- Assess the patient for signs and symptoms of under- and overreplacement at each visit.
- Monitor for and prevent drug-drug interactions.
- Identify the most vulnerable thyroid disease patient populations with the greatest risk of adverse outcomes with inconsistent thyroid hormone replacement therapy.

Page 1-179

Case #2

- Mrs. L. is a 38-year-old woman with newly diagnosed Graves' disease who experiences fatigue, heat intolerance, tremor, and palpitations. She has no significant medical history and is currently taking no medications. Laboratory results include the following: TSH less than 0.01 mIU/L (0.4–4); FT4 3.3 ng/dL (0.7–1.9); and TT3 368 ng/dL (80–180). Initiation of which one of the following regimens will reduce her symptoms within hours?

A. PTU 100 mg 3 times/day
B. Methimazole 10 mg 2 times/day
C. Lugol's solution 10 drops 3 times/day
D. Nadolol 40 mg 2 times/day

Workbook Page 1-180; Answer: Page 1-214.

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C. Lugol's solution 10 drops 3 times/day
D. Nadolol 40 mg 2 times/day

Workbook Page 1-180; Answer: Page 1-214.

Polycystic Ovary Syndrome Clinical Pearls

- PCOS is the most common endocrinopathy in reproductive-age women, with an estimated prevalence of 5%–10%; affecting 6–7 million women.
- PCOS is associated with a high risk of infertility (75%) and is the most common pathologic cause of anovulation.
- PCOS is associated with a higher risk of endometrial cancer compared with age-matched women without PCOS.
- Because of insulin resistance, PCOS is associated with higher risks of metabolic syndrome, HTN, dyslipidemia, type 2 DM, and cardiovascular disease compared with women without PCOS. Also a greater incidence of obstructive sleep apnea and depression.

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PCOS - Pathophysiology

- Hypothalamus-pituitary-ovarian abnormality Ovarian-induced increase in gonadotropin-releasing hormone results in abnormal increase in LH/FSH ratio with resulting increase in ovarian testosterone production.
- Insulin resistance
  - Increase in endogenous insulin levels caused by insulin resistance in muscle and adipose tissues results in excess androgen production by the ovaries (which remains sensitive to insulin), causing increased testosterone production.
  - Excess insulin also decreases hepatic synthesis of sex hormone–binding globulin (SHBG), which normally binds free testosterone, resulting in increased hirsutism.

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PCOS - Clinical Presentation

- Chronic anovulation most often manifesting as oligomenorrhea (fewer than nine menses per year) or amenorrhea. Anovulatory cycles may lead to dysfunctional uterine bleeding, decreased fertility, and a higher prevalence of endometrial hyperplasia and carcinoma.
- Cutaneous manifestations of hyperandrogenemia
  - Hirsutism (hair on sternum, upper abdomen, or upper back compared to upper lip or areolae)
  - Acne
  - Male pattern hair loss (androgenic alopecia); other virilizing features such as clitormegaly and increased muscle bulk suggest an alternative diagnosis
- Hyperandrogenemia (e.g., elevated levels of total or free testosterone/ androstenedione)
- Characteristics of insulin resistance
  - Acanthosis nigricans (raised velvety brown discoloration on nape of neck, axilla, knuckles, elbow)
  - Overweight/obese (especially increased visceral adiposity)
  - 40% with impaired glucose tolerance, 10% with type 2 DM by age 40 (because of insulin resistance an OGTT is recommended for all women with PCOS and a BMI greater than 27)
  - Nonalcoholic steatohepatitis (NASH)
  - Higher risk of coronary artery disease, HTN, low high-density lipoprotein cholesterol, high triglycerides, and obstructive sleep apnea
- Abdominal obesity
- Symptoms typically begin around menarche

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PCOS - Diagnosis

- At least two of the following are present:
  - Oligoovulation or anovulation (usually manifested as oligomenorrhea or amenorrhea)
  - Elevated levels of circulating androgens (hyperandrogenemia) or clinical manifestations of androgen excess (hyperandrogenism)
  - Polycystic ovaries as defined by ovarian ultrasonography (transvaginal) - $\geq$ 12, 2-9 mm diameter follicles in each ovary or increased ovarian volume (>10cm^3)
- Other causes must be ruled out (hyperprolactinemia, nonclassic congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting neoplasm, acromegaly, HoTR, pregnancy).

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PCOS - Goals of Treatment

- Improve symptoms and quality of life.
- Increase fertility (for most women).
- Prevent concomitant morbidity

Page 1-181

PCOS - Treatment

- Pharmacist role in patient care/monitoring
  - Educate patient regarding disease and appropriate lifestyle modifications.
  - Encourage patient adherence.
  - Develop a plan to assess effectiveness of medications/lifestyle modifications.
  - Monitor for drug adverse effects and drug-drug interactions.
- No single drug treats the entire PCOS. Treatment focuses on the management of the complication/concern and should be individualized. Determine whether the patient seeks pregnancy or not and proceed from there.
- Lifestyle modifications—Improve all PCOS-specific complications
  - Weight loss: Modest reductions in body weight (5%–7%) through lifestyle modification have been associated with reductions in androgen levels and improved ovulatory function.
  - Exercise: Aerobic exercise decreases insulin resistance (regardless of weight loss).

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Treatment by PCOS-specific Concern

- Infertility
  - Weight loss
  - Clomiphene (Clomid, Serophene)—Recommended for patients wishing to become pregnant; an antiestrogen that induces a rise in FSH and LH, resulting in ovulation
    - Dose: 50–100 mg/day for 5 days initiated on day 5 of cycle
    - Adverse effects: hot flashes, breast discomfort, ovarian hyperstimulation syndrome, abdominal distention/bloating
    - CIs: pregnancy, liver disease. Increased likelihood of multiple births
  - Metformin: Decreases endogenous insulin levels by inhibiting hepatic glucose production; the lower insulin concentration results in the reduction of androgen production by ovarian theca cells with a 4-fold increased potential of ovulation
    - Dose: 1–2 g/day: Improves blood glucose & lipid profile. Lowers rates of spontaneous miscarriage and gestational diabetes who conceive while taking metformin.

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Treatment by PCOS-specific Concern

- Hyperandrogenism/Hirsutism
  - Local measures: shaving, waxing, depilatories, lasers and electrolysis
  - Oral contraceptives
    - Estrogen–progestin combination ideally with a nonandrogenic progestin (norgestimate, desogestrel, drospirenone [e.g., Yaz])
    - Controls hirsutism and acne, is effective treatment of oligomenorrhea and amenorrhea, and protects against unopposed estrogenic stimulation of the endometrium
    - Potential adverse effects on insulin resistance and glucose tolerance, vascular reactivity, and coagulability are concerns.
  - Spironolactone
    - Possesses moderate antiandrogenic effects when administered in large doses (100–200 mg/day); decreases adrenal androgen production; use with OC as risk for pregnancy (feminization of male infants) and breakthrough bleeding
    - Spironolactone and oral contraceptives appear to be synergistic.

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Treatment by PCOS-specific Concern

- Hyperandrogenism/Hirsutism (con't)
  - Metformin
  - Eflornithine (Vaniqa)
    - Inhibits ornithine decarboxylase, leading to a decreased rate of hair growth
    - Use of hair removal techniques is still required.
    - 13.9% cream applied to affected areas of face 2 times/day (8 hours apart)
    - Do not wash skin for 8 hours after application.
    - Adverse effects include pruritus, burning/tingling skin, dry skin, and rash.
  - Flutamide
    - Potent nonsteroidal antiandrogen, inhibits binding of androgen in target tissue; 250 mg once daily; hepatotoxicity concerns limit its use (check liver function tests [LFTs] monthly for first 4 months and then periodically); CIs include liver disease and pregnancy; adverse effects include the following: hot flashes, galactorrhea, nausea
  - Cyproterone
    - Antiandrogen
    - Often used in combination with OCs
    - Decreased libido, tiredness, and LFT changes
  - Topical minoxidil (2-5%) for alopecia

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Treatment by PCOS-specific Concern

- Insulin Resistance
  - Metformin
  - Pioglitazone (Actos)
    - Insulin sensitizer that results in the reduction of androgen production by ovarian theca cells; this also results in a greater likely of ovulation
    - Improves blood glucose
    - Lowers plasminogen activator inhibitor 1 levels
    - Increases HDL-C
    - Doubles serum adiponectin levels
    - Concerns about use of TZD use during pregnancy, so not considered first line
    - 15–45 mg orally daily
      - Adverse effects include edema and weight gain

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Treatment by PCOS-specific Concern

- Menstrual Irregularities
  - Oral contraceptive
- Endometrial Hyperplasia
  - Oral contraceptive
  - Progestin challenge if > 3 months of amenorrhea; endometrial biopsy if ≥ 1 yr or if endometrial thickness on ultrasound is > 14 mm

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Polycystic Ovary Syndrome Utility of Individual Treatment Choices

Table 1.

Drug	Use			
	Hirsutism or Acne	Oligomenorrhea Amenorrhea	Ovulation Induction	Insulin Lowering
Oral contraceptives	X	X		
Spironolactone	X			
Flutamide	X			
Clomiphene			X	
Metformin	X	X	X	X
Pioglitazon	X	X	X	X

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Case #3

- Molly is a 26-year-old white woman with PCOS, HTN, and hyperlipidemia. She is most bothered by her irregular periods. At this time, she is not interested in starting a family. Which one of the following choices is best suited for Molly?

- A. Spironolactone
- B. Flutamide
- C. Ethinyl estradiol and desogestrel (Apri)
- D. Pioglitazone

Workbook Page 1-184; Answer: Page 1-214.

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Workbook Page 1-184; Answer: Page 1-214.

Pituitary Disease - Clinical Pearls

- Prolactinomas represent the most common type of pituitary tumor and the fifth most common endocrine disorder.
- Prolactin is the erythrocyte sedimentation rate of the hypothalamus.
- Drug-induced hyperprolactinemia is associated with prolactin concentrations of less than 100 ng/mL.
- Multiple endocrine neoplasia type 1 syndrome (MEN1): The three P's (pituitary, parathyroid, and pancreas)
- Growth hormone (GH) excess in childhood results in giantism; GH excess in adults results in acromegaly.

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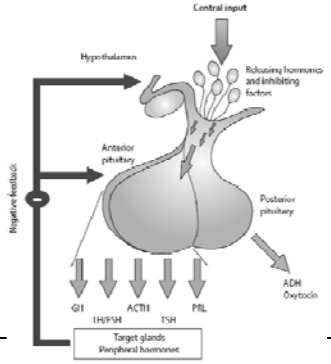
Normal Pituitary Gland Hormone Secretion



Schneider HJ et al. Lancet. 2007;369:1461-70.

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Prolactinomas

- Prolactinoma
  - Pituitary tumor (adenoma) that secretes excessive amounts of prolactin
  - Prolactin is the hormone that stimulates milk production by the breasts; secreted by lactotroph cells of the anterior pituitary; its production is typically under the inhibitory control of dopamine
  - Represents the most common type of pituitary tumor
  - Represents the 5th most common endocrine disorder
  - May exist "silently" in 5% of the adult population
  - Micro- versus macroadenoma
- Hyperprolactinemia
  - Prolactin level greater than 30 ng/mL
  - Normal prolactin level: 15–25 ng/mL

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Causes of Hyperprolactinemia

- High Levels (> 200 ng/mL)
  - Prolactin-secreting tumor
- Modest Elevations (30–100 ng/mL)
  - Pregnancy (early)/lactation
  - Stress (discomfort, exercise, low blood glucose)
  - Hypothyroidism
  - Kidney failure
  - Liver failure
  - Medications
  - "Stalk" Effect

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Drug-Induced Hyperprolactinemia

- Typically associated with levels < 100 ng/mL
- Drugs
  - Dopamine antagonists
    - (a) Phenothiazines/antipsychotics
    - (b) Tricyclic antidepressants
    - (c) Metoclopramide
  - Selective serotonin reuptake inhibitors
  - Estrogen-progesterone
  - Methyldopa
  - Verapamil
  - Gonadotropin-releasing hormone analogs (leuprolide, goserelin, naferelin)

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Hyperprolactinemia - Clinical Presentation

- Women
  - Typically of reproductive age; present early in course of adenoma
  - Irregular menstrual periods or amenorrhea
  - Infertility
  - Galactorrhea
  - Reduction in sex drive
  - Vision loss/headache possible (microadenoma)
  - Osteoporosis (long-term)
- Men
  - Present in 50s and 60s, more likely to have macroadenoma, present late
  - Manifestation of sex hormone production decrease
    - Decreased libido
    - Erectile dysfunction
    - Loss of body hair
  - Vision loss/headache more likely (macroadenoma)
  - Osteoporosis (long term)

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Hyperprolactinemia - Diagnosis

- Signs or symptoms
- Elevated prolactin level (> 30 ng/mL)
- Imaging studies (MRI, CT) of the pituitary gland
- Find cause
- Consider complete pituitary hormone evaluation (especially macroprolactinomas)

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Hyperprolactinemia - Treatment

- Drug Therapy – D2 Receptor Agonist
  - Bromocriptine (Parlodel)
    - Generic
    - Higher incidence of nausea; preferred for fertility
    - Initiate at 1.25 mg once daily or 2 times/day (with meal); increase weekly; maximal dose 15 mg/day
    - May consider taper and discontinuation of therapy after 2–3 years of normal prolactin levels in patients with microadenomas; continue to monitor prolactin levels every 6–12 months
    - Drug-drug interactions: 3A4 inhibitors (ritonavir, indinavir, ketoconazole, itraconazole, clarithromycin)
    - CIs: Patients with ischemic heart disease, peripheral vascular disease, and uncontrolled HTN
  - Cabergoline (Dostinex)
    - May be effective in patients whose prolactinomas are resistant to bromocriptine therapy
    - Better GI tolerance
    - Initiate at 0.25 mg twice a week; maximal dose of 1 mg twice weekly
    - May consider taper and discontinuation of therapy after 2–3 years of normal prolactin levels in patients with microadenomas; continue to monitor prolactin levels every 6–12 months
    - Drug-drug interactions: 3A4 inhibitors (ritonavir, indinavir, ketoconazole, itraconazole, clarithromycin)
    - CIs: Patients with ischemic heart disease, peripheral vascular disease, and uncontrolled HTN

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Hyperprolactinemia - Treatment

- Transsphenoidal surgery: Reserved for patients resistant to or intolerant of pharmacologic therapy; microadenomas have better response rate than macroadenomas
- Radiotherapy: Reserved for patients resistant to or intolerant of pharmacologic therapy and surgery; normalization of prolactin levels may take years; risk of radiation-induced hypopituitarism
  - Stereotactic radiation (gamma knife)
  - External beam radiation

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Case #4

- A 27-year-old woman is referred to an endocrinologist by her gynecologist after experiencing irregularities in her menstrual cycle. The following laboratory data are revealed: TSH of 1.9 mIU/L (nl 0.4–4) and prolactin level of 247 ng/mL (nl 15–25). A subsequent MRI of the pituitary identifies a 6-mm adenoma. She is interested in starting a family as soon as possible. Which one of the following therapies is best for this patient?

[ ] A. Bromocriptine 1.25 mg 2 times/day.
[ ] B. Cabergoline 0.25 mg twice weekly.
[ ] C. Clomiphene 50 mg once daily for 5 days.
[ ] D. Metformin 1000 mg 2 times/day

Workbook Page 1-187; Answer: Page 1-214.

Case #4

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D. Metformin 1000 mg 2 times/day

Workbook Page 1-187; Answer: Page 1-214.

Sandy Allen World's Tallest Woman

Growth Hormone Excess - Causes

- Pituitary adenoma (cause of greater than 95% of all cases)
- Rarely caused by tumors of the pancreas, lung, ovary, or breast (ectopic GH or GH-RH secreting)
- May be part of the MEN1 syndrome
  - Pituitary tumor
  - Parathyroid hyperplasia
  - Pancreatic tumor (gastrinoma or insulinoma)

Acromegaly - Clinical Presentation

- Children (Giantism) vs. Adults (Acromegaly)
- Enlarged hands and feet (new ring/shoe size)
- Excessive sweating
- Coarse facial features
- Multiple skin tags
- Deepened voice
- Osteoarthritis
- Sleep apnea
- Headache/Visual disturbances
- Increased risk of DM, colonic polyps, colon cancer, and coronary artery disease

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Acromegaly - Diagnosis

- Elevated insulin-like growth factor 1 (IGF-1) (somatomedin C) levels
  - ideal screening test
  - normal levels vary with sex and age
- Elevated serum GH level in the fasting state and after an OGTT (normals suppress GH to less than 1 ng/mL after OGTT)
- MRI with special cuts of the pituitary showing a pituitary tumor
- Check old photographs

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Growth Hormone Excess

Acromegaly - Treatment Goals

- Relieve symptoms
- Normalize IGF-1 levels (for age and sex) and GH level less than 1 ng/mL after glucose challenge
- Preserve normal pituitary function
- Reduce mortality (cardiovascular, pulmonary, and oncologic causes)

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Acromegaly - Treatment

- Transsphenoidal surgery (find an experienced neurosurgeon!)
  - TOC for most patients with GH-producing adenomas
  - 75% efficacy in microadenomas, less than 50% in macroadenomas
  - Potential of postsurgical pituitary injury (e.g., pan-hypopituarism)
- Stereotactic radiosurgery
  - Typically reserved for macroadenomas that have invaded neighboring tissues and nerves (reserved for patients with residual GH excess after surgery or pharmacotherapy)
  - Full effect not seen until months to years later
  - High risk of hypopituitarism
- Drug therapy
  - Used when surgery is contraindicated or has failed
  - Dopamine agonists, somatostatin analogs, GH receptor antagonist

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Acromegaly - Treatment

- Octreotide and Octreotide LAR (Sandostatin, Sandostatin LAR)
  - Mechanism of action
    - Somatostatin analog; binds to somatostatin receptors and causes direct inhibition of GH secretion
    - Long-term treatment can reverse some soft tissue manifestations of disease.
    - Reduces tumor size
  - Dosing
    - Octreotide
    - 50–100 mcg subcutaneously every 8–12 hours
    - Can switch to octreotide LAR, 20 mg intramuscularly every 4 weeks
    - Dose to GH levels less than 1 ng/mL and IGF-1 levels less than 2 units/mL.
  - Adverse effects
    - GI: Diarrhea, Nausea, GI cramps
    - Fever
    - Dizziness
    - Hyper or hypoglycemia (alters the balance of counter-regulatory hormones)
    - Cholelithiasis (inhibits gallbladder contractility)
    - Hypothyroidism (rare; may suppress pituitary release of TSH)
  - Drug interactions
    - Cyclosporine, β-Blockers, Calcium channel blockers
  - Efficacy
    - 95% of patients with symptom relief
    - Two-thirds of patients will normalize IGF-1 levels.

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Acromegaly - Treatment

- Lanreotide SR and Lanreotide Autogel (Somatuline Depot)
  - Synthetic analog of somatostatin
  - Slow Release
    - Start with 60 mg intramuscularly every 2 weeks and titrate
  - Depot
    - 90 mg deep subcutaneously every 4 weeks for 3 months; then adjust dose on the basis of GH and IGF-1 levels

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Acromegaly - Treatment

- Pegvisomant (Somavert)
  - Mechanism of action
    - GH receptor antagonist; blocks the binding of endogenous GH, leading to
  - decreased IGF-1 levels
    - Used in patients resistant to or intolerant of octreotide
    - Use is not associated with a reduction in tumor size.
  - Dosing
    - A 40-mg subcutaneous loading dose; then 10 mg subcutaneously once daily
    - Increase by 5 mg increments at 4- to 6-week intervals on the basis of IGF-1 levels (maximum 30 mg/day)
  - Adverse effects
    - Headache
    - Diarrhea
    - Nausea
    - Increase in LFTs
    - Hyperglycemia
    - Flu-like symptoms

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Acromegaly – Treatment (cont.)

- Efficacy
  - 95% of patients with symptom relief
  - 95% of patients will normalize IGF-1 levels.
  - Use may be associated with increase in tumor size.
- Other
  - Drug is a modified GH; it interferes with GH level measurements (detected in GH assay, overestimates true GH levels).
  - Monitor LFTs monthly for 6 months and then every 6 months.
  - MRI of pituitary every 6 months (because of concern about tumor growth)
  - Dopamine agonists (bromocriptine, cabergoline)—Relative lack of efficacy

Follow-up Monitoring

- Improvement of symptoms and soft tissue changes
- OGTT-stimulated GH levels q 6-12 months
- IGF-1 levels q 6-12 months
- Consider repeat of pituitary MRI annually
- Assess pituitary function annually (e.g., TSH, ACTH, FSH/LH)
- Colonoscopy
- Address CV risk factors

Case #5

- Brad is a 54-year-old man who has had transphenoidal surgery to remove a GH-secreting pituitary adenoma. His GH and IGF-1 levels remain elevated 3 months later. Which of the choices is the best initial drug treatment for his acromegaly?

A. Genotropin
B. Sandostatin
C. Somavert
D. Humatrope

Workbook Page 1-190; Answer: Page 1-214.

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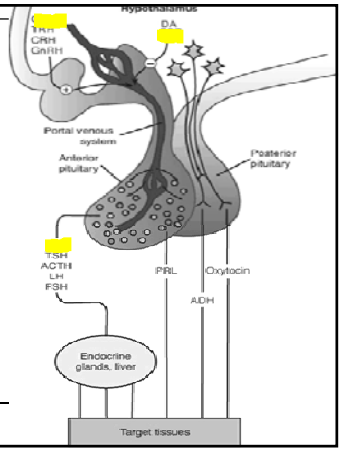
Workbook Page 1-190; Answer: Page 1-214.

Hypothalamic -Pituitary Endocrine System



Master SB. In: Basic and Clinical Pharmacology. 11th Ed, 2009; Chapter 37, page 644.

Growth Hormone Deficiency

- Causes
  - Idiopathic
  - Pituitary injury (tumor, surgery, radiation therapy, trauma, infection)

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Growth Hormone Deficiency Clinical presentation

- GHD in children (Short Stature)
  - Height of two standard deviations or more below age- and sex-matched population means and below the third percentile for height in a specific age group
  - Central obesity/low muscle mass
  - Decreased growth velocity/ delayed skeletal maturation
- GHD in adults
  - Lethargy and fatigue
  - Central obesity/low muscle mass
  - Decreased strength
  - Decreased bone mineral density
- 1.8 million children in US with short stature
  - Estimated 1 in every 10,000-15,000 children
- 2 million adults in US with GHD

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Growth Hormone Deficiency

- Diagnosis
  - Rule out other causes of growth delay (malnutrition, HoTR).
  - Low GH levels (< 10 ng/mL) following GH provocation test (insulin, arginine).
  - Low insulin-like growth factor 1 (IGF-1) levels (two standards below the standard reference range).

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Growth Hormone Deficiency

- Therapy Goals
  - Achieve normal adult height (in children)
    - Initiation at an early chronologic age and prior to onset of puberty associated with greatest increase in height
  - Increase muscle mass/reduce adiposity

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TABLE 1. FDA-approved indications for human GH

Year of FDA approval[a]	Indication	Recommended doses[b]
1985	GH deficiency	0.16–0.3 mg/kg · wk (up to 0.7 mg/kg · wk approved in pubertal patients)
1993	Chronic renal insufficiency	Up to 0.35 mg/kg · wk until renal transplantation
1996	Turner syndrome	0.33 mg/kg · wk; other approved doses are up to 0.375 or 0.469 mg/kg · wk
1997	Adult GH deficiency	FDA-approved starting dose, schedule for dose increase, and maximum doses vary[c]
2000	Prader-Willi syndrome	0.24 mg/kg · wk
2001	Small for gestational age (and failure to manifest catch-up growth by 2–4 yr)	0.33 mg/kg · wk; other approved dose ranges are 0.231–0.469 mg/kg · wk based on initial height and response to treatment and up to 0.48 mg/kg · wk
2003	Idiopathic short stature	Approved doses are up to 0.3 mg/kg · wk, 0.37 mg/kg · wk, and, and 0.47 mg/kg · wk
2003	Short bowel syndrome in patients receiving specialized nutritional support (no pediatric studies when approved)	0.1 mg/kg · d (0.7 mg/kg · wk), up to a maximum of 8 mg/d; administration for more than 4 wk was noted not to have been adequately studied
2003	HIV patients with wasting or cachexia (adults)	From 0.1 mg/kg · d (0.7 mg/kg/wk) if < 35 kg to 6 mg/d if ≥55 kg
2006	SHOX (short stature homeobox-containing gene) deficiency	0.35 mg/kg · wk
2007	Noonan syndrome	Up to 0.066 mg/kg · d (i.e. 0.469 mg/kg · wk)

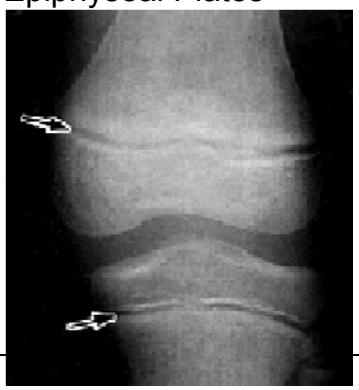
Unless otherwise stated, data in table refer to children with short stature. Current nonapproved uses of GH in children are cystic fibrosis, steroid-mediated growth failure, HIV, and inflammatory bowel disease.

[a] Year of initial approval by the FDA for the designated indication. Subsequently, the FDA may have approved other GH products for the designated indication. The reader is referred to www.fda.gov/Drugs/InformationonDrugs (drug approvals and databases) for additional information.

[b] Doses shown are based on all GH products with FDA approval for the designated indication. Where there is a wide range of doses, the range is indicated. Data were provided by the FDA. Average wholesale price for most innovator brands of GH is approximately $76/mg and $55/mg for biosimilar GH (www.Americourcebergen.com; January 23, 2010).

[c] Issues related to dosing for adult GH deficiency are summarized in The Endocrine Society Clinical Practice Guideline (www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm (Evaluation and Treatment of Adult GH Deficiency).

Open Epiphyseal Plates



GH Deficiency - Treatment

- Somatropin (Recombinant GH) - Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Serostim, Tev-Tropin, Zorbtive)
  - Dosing
    - Administer in the evening; Nutropin Depot 1-2/month SQ
    - Children: 0.175–0.35 mg/kg/week given as daily, twice weekly or 3 times/week subcutaneous injections; minimum 5 cm/year linear growth expected.
      - Dose Increases
      - Drug Discontinuation
    - Adults: Lower doses, typically non-weight based, recommended; 0.2 mg/day
  - Contraindications
    - Active malignancy

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Growth Hormone Deficiency

- Adverse effects
  - Seen more commonly in adults
  - Fluid retention, increased SBP, increased average glucose concentration
  - Carpal tunnel syndrome
  - Arthralgias, Myalgias
  - Intracranial HTN (rare)
- Monitoring
  - Growth curve, Tanner staging, and bone age every 6-12 months
  - TFT's, glucose, IGF-1 levels
  - Fundoscopic exam
  - Height

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Growth Hormone Deficiency - Other Treatments

- Recombinant IGF-1 products
  - Mecasermin (Increlex)
    Recombinant Insulin-like Growth Factor-1
  - Mecasermin rinfabate (Iplex)
    Recombinant Insulin-like Growth Factor-1 with IGFBP-3
- Recombinant Growth Hormone Releasing Hormone
  - Semoralin (Geref)

Obesity - Clinical Pearls

- Better living through BETTER LIVING
- Obesity is a lifelong disease.
- Weight loss is hard; weight maintenance is HARDER.
- Patients need achievable goals and expectations.
- A good pharmacist motivates, supports, encourages, empathizes, advocates, and does not judge.
- Obesity studies typically have 30–40% patient dropout rates.
- One pound of fat equals 3500 calories.
- Goal weight loss is typically 1–2 lb/week until target weight is met.
- U.S. Food and Drug Administration (FDA)-approved medications combined with changes in lifestyle result in a 3%–5% greater weight loss (3–5 kg) compared with changes in lifestyle and placebo.
- Because there is no single cause of overweight and obesity, there is no single way to prevent or treat overweight and obesity that will help everyone.

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The Scope of the Problem

- More than two-thirds of adults in the United States are overweight or obese, and more than one-third are obese (NHANES 2003–2006 and 2007–2008).
- Overweight and obesity are associated with many coexisting conditions, including HTN, glucose intolerance, dyslipidemia, and obstructive sleep apnea.
- Obesity is associated with an increased risk of death from CV disease, diabetes, kidney disease, and some cancers (colon, breast, esophageal, uterine, ovarian, kidney, and pancreatic).

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Classification

- Body Mass Index
  - Underweight: BMI < 18.5 kg/m^2
  - Normal weight: BMI 18.5 – 24.9 kg/m^2
  - Overweight: BMI 25 – 29.9 kg/m^2
  - Obesity (Class 1): BMI 30 – 34.9 kg/m^2
  - Obesity (Class 2): BMI 35 – 39.9 kg/m^2
  - Extreme Obesity (Class 3): BMI $\geq$ 40 kg/m^2
- Waist Circumference
  - Greater than 40 inches in Men
  - Greater than 35 inches in Women
- Waist/Hip Ratio
  - Greater than 1.0 in Men
  - Greater than 0.8 in Women

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Do You Know Your Own BMI?

Height	Weight (lbs)																				
	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39
6'4"	15	16	17	18	20	21	22	23	24	26	27	28	29	30	32	33	34	35	37

Risk Factors of Overweight and Obesity

- Type 2 DM
- Coronary artery disease
- High LDL-C
- Stroke
- Hypertension
- Nonalcoholic fatty liver disease
- Gallbladder disease
- Sleep apnea
- Osteoarthritis
- Polycystic ovary syndrome
- Physical inactivity

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Medications Associated with Weight Gain

- Insulin
- Thiazolidinediones
- Sulfonylureas
- Antipsychotics (especially atypicals)
- TCA's/SRI's
- Lithium
- Valproic acid
- Glucocorticoids
- Oral contraceptives
- Medications associated with edema: Gabapentin, pregabalin, nonsteroidal anti-inflammatory drugs, dihydropyridine calcium channel blockers

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Treatment Goals

- Prevent additional weight gain.
- Reduce weight and maintain weight loss.
- Control concomitant risk factors.
- Prevent obesity-related health problems and mortality.

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Case #6

H.K. is a 52-year-old Hispanic woman receiving an orthopedic consultation regarding the pain in her knees caused by osteoarthritis. She is 5′2″ tall and weighs 245 lb. She is unable to ambulate without significant bilateral knee pain. Her medical history is also significant for type 2 DM, HTN, dyslipidemia, gout, depression, and sleep apnea. Her current medications include indomethacin, metformin, pioglitazone, hydrochlorothiazide (HCTZ), losartan, atorvastatin, niacin, allopurinol, aspirin, and nortriptyline. Which one of the following is the best recommendation for this patient?

- A. Stop taking medications that can cause weight gain (indomethacin, pioglitazone, nortriptyline).
- B. Initiate a running regimen to lose 7% of body weight.
- C. Go to a bariatric specialist.
- D. Begin orlistat 120 mg 3 times/day with meals.

Workbook Page 1-193; Answer: Page 1-214.

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Workbook Page 1-193; Answer: Page 1-214.

General Treatment Principles of Obesity/Overweight Management

- Lifestyle changes - Recommended for BMI >30 kg/m2 or BMI greater than 25–30 kg/m2 with comorbidities
  - Diet modification

    Diet Composition vs. Total Calories

    Short-term (6–12 months) benefits sustained long-term?
    - Low fat
      - Ornish
      - Very low-fat diets have been associated with slowing or reversing atherosclerosis.
    - Low carbohydrate
      - Atkins (high protein and high fat)
      - South Beach
    - Very low-calorie diets
      - Total energy intake below 800 kcal/day
      - High attrition rates and weight rebound

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General Treatment Principles of Obesity/Overweight Management

- Diet modification
  - Balanced-deficit
    - Zone
    - Weight Watchers
  - Particular food type
    - Low glycemic index
    - The Diet, Obesity, and Genes (Diogenes) study
    - Low-energy-density diet
  - Highlight specific foods: Grapefruit
  - Portion control diets: Portion size is controlled by manufacturer of frozen meals, breakfast bars, or beverages used at breakfast and/or lunch (meal and snack replacement).
  - Commercial and Self-help programs
    - Overeaters Anonymous
    - TOPS (Take Off Pounds Sensibly)
    - Weight Watchers
    - Jenny Craig
    - Herbalife
    - OPTIFAST
    - LA Health
    - e-Diets

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General Treatment Principles of Obesity/Overweight Management

- Diet modification
  - Adjuncts to effective dietary management
    - Eating breakfast
    - Adding dietary fiber
    - Eating at regular meal intervals
    - Use of meal replacements (e.g., Slim-Fast)
    - Involvement of dieticians
    - Limit consumption of sugary beverages.
    - Increase number of daily fruit and vegetable servings.
    - Limit restaurant/fast food meals.
  - Tailoring diet therapy
    - Higher satiety with high-protein, high-fiber diet
    - Low-fat diet for patient with hyperlipidemia
    - Avoid high-protein diets in patients with renal disease.

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General Treatment Principles of Obesity/Overweight Management

- Exercise (or any enhanced physical activity)
  - A different approach for balancing energy intake and expenditure 30–60 minutes/day, 5 days/week generally recommended
  - Exercise alone is typically inadequate as primary treatment for weight loss.
  - Use of pedometers (about 2000 steps equals 1 mile)
  - All or none phenomenon
- Behavioral modifications
  - Keeping a food diary
  - Identifying situations that trigger eating
  - Allows patients to change eating habits and adopt a defined eating plan

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Snow V, et al. Ann Intern Med 2005;142:525–31.

Figure 1. Algorithm for managing obesity.

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Pharmacologic Treatment - Tenets of Therapy

- Consideration in patients
  - BMI greater than 30 kg/m^2 and no associated diseases or BMI greater than 27 kg/m^2 with co-morbidities
  - Who do not meet individualized goals with counseling on lifestyle and behavior modifications.
- Pharmacists should discuss the limitations and adverse effects of available drugs with patients.
- Drug therapy should only be used as part of a complete program including diet, lifestyle change, and regular physical activity

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Pharmacologic Treatment Diethylproprion (Tenuate)

- Mechanism of Action
  - Sympathomimetic (increases norepinephrine and dopamine release in the central nervous system thus decreasing appetite)
- Efficacy
  - Short-term efficacy; 3- to 4-kg weight loss
- Dose
  - 25 mg 3 times/day with meals or 75 mg controlled release q AM
- Adverse Effects
  - Dry mouth
  - Constipation
  - Insomnia
  - Asthenia

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Pharmacologic Treatment Diethylproprion (Tenuate)

- Contraindications
  - Monoamine oxidase inhibitor (MAOI) use within 14 days
  - Pulmonary HTN
  - Hyperthyroidism
  - Coronary artery disease
  - Glaucoma
  - History of substance abuse
- Drug-Drug Interactions
  - MAOI use within 14 days
  - Other sympathomimetics
- Other
  - High abuse potential
  - FDA schedule: IV

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Pharmacologic Treatment
Phentermine (Ionamin, Adipex-P)

- Mechanism of Action
  - Sympathomimetic; suppresses appetite
- Efficacy
  - Short-term efficacy; 3- to 4-kg weight loss
- Dose
  - 15–37.5 mg 3 times/day before meals
  - 15–30 mg every morning (resin)
- Adverse Effects
  - Palpitations, tachycardia
  - Elevated blood pressure
  - Dry mouth
  - Constipation
  - Insomnia
  - Asthenia
  - Pulmonary HTN and valvular heart disease seen in combination with fenfluramine or dexfenfluramine (Phen-Fen)

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Pharmacologic Treatment
Phentermine (Ionamin, Adipex-P)

- Contraindications
  - MAOI use within 14 days
  - History of heart failure, cardiovascular disease, arrhythmias, stroke, or glaucoma
  - Safety and efficacy have not been established in patients younger than age 16.
- Drug-Drug Interactions
- Other
  - Most commonly prescribed antiobesity agent
  - Often used in combination with other drugs
  - Short-term (12 weeks) use approved only
  - High abuse potential
  - FDA schedule IV

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Pharmacologic Treatment
Orlistat (Xenical, Alli)

- Mechanism of Action
  - Gastric and pancreatic lipase inhibitor; reduces absorption of dietary fat (approximately 30%)
- Efficacy
  - 3 to 4-kg weight loss
- Dose
  - 60 mg(over the counter) or 120 mg (prescription) 3 times/day with meals (containing fat)
- Adverse Effects
  - GI adverse effects: caused by malabsorption of fat (oily spotting, flatus with discharge, fecal urgency, fecal incontinence—but no diarrhea); bloating, and cramping

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Pharmacologic Treatment
Orlistat (Xenical, Alli)

- Contraindications
  - Chronic malabsorption syndrome
  - Cholestasis
  - Safety not established in pregnant or lactating women
- Drug-Drug Interactions
  - Fat-soluble vitamins
  - Cyclosporine
  - Warfarin
- Other
  - Because of the potential for fat-soluble vitamin (ADEK) deficiency, daily multivitamin use is required (2 hours before or after orlistat)
  - FDA schedule: Nonscheduled
  - 30%–40% discontinuation rate
  - Use is associated with twice the LDL-C reduction expected with weight loss alone.

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Pharmacologic Treatment
Natural and Herbal Products

- Chromium picolinate
- Ephedra
- Green tea extract
- Bitter orange
- Guar gum

Page 1-197

Approved Medications with Weight-loss Properties (not approved for weight loss)

- Exenatide (Byetta)
- Liraglutide (Victoza)
- Pramlintide (Symlin)
- Topiramate(Topamax)
- Lamotrigine (Lamictal)
- Zonisamide (Zonegran)
- Fluoxetine (Prozac)
- Bupropion (Wellbutrin, Zyban)

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Pharmacologic Treatment Investigational Agents

- Phentermine/topiramate (Qnexa)—originally rejected by the FDA 10/29/10 because of safety concerns (birth defects and heart problems); but Endocrinologic and Metabolic Drugs Advisory Committee voted 20-2 in favor on Feb 22, 2012. Also urged the agency to require a post-approval trial to monitor for cardiovascular side effects.
- Naltrexone and bupropion (Contrave)— Rejected by FDA Feb 1 2011due to safety concerns; has asked for a long-term study to demonstrate that the drug does not raise the risk of MI (increases pulse rate and BP)
- Lorcaserin (Lorqess)—Serotonin-2C agonist; rejected by the FDA 10/21/10; caused tumors in rats
- Tesofensine—Combined multi-amine reuptake inhibitor
- Rimonabant—Cannabinoid receptor blocker; approved and marketed in Europe but not approved by the FDA because of increased incidence of depression and anxiety

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Surgical Treatment

- Historically, recommended for BMI greater than 40 kg/m^2 or BMI greater than 35 kg/m^2 with comorbidities (DM, sleep apnea, cardiovascular disease, joint disease).
- Gastric bypass
  - A 30- to 40-kg weight loss maintained for 10 years
  - Decreased morbidity and mortality
  - Demonstrated to reverse T2DM
  - Serious nutritional deficiencies associated—Iron, B12, folate, calcium
  - 0%–1% risk of postsurgical mortality (refer to bariatric surgeon who performs these procedures frequently)
- Laparoscopic adjustable gastric banding
  - A 20- to 30-kg weight loss maintained for 5 years
  - Decreased morbidity and mortality
  - Approved 1/11 in BMI of 30 - 40 and at least one obesity-related comorbidity, such as diabetes.
- Liposuction
  - No significant improvements in metabolic or cardiac risk factors
  - Not recommended for weight loss

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Patient Advocacy

- U.S. Preventive Services Task Force
  - Recommends clinicians screen all adult patients for obesity and offer intensive counseling
  - Recommends behavioral interventions to promote sustained weight loss for obese adults
- Pharmacists' roles
  - Encourage healthy habits—Eat breakfast, limit high-sugar foods and drinks, reduce sedentary activities, monitor food intake, increase physical activity
  - Run obesity screening programs.
  - Work with prescribers in weight-loss clinics.
  - Counsel patients regarding drugs that can contribute to weight gain.
  - Provide patients with diet and exercise counseling.
  - Help patients set realistic weight-loss goals.
  - Explain the advantages/disadvantages of lifestyle changes versus medications versus surgery.
  - Work with patients on a long-term basis to help them achieve these goals.

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Case #7

A 32-year-old woman is seen for a routine annual physical examination. She states she would like to lose weight. She works as a librarian and is physically active, walking for 30 minutes 2 or 3 times/week. She does not smoke, but she drinks alcohol socially (seldom more than 2 drinks per week). She has been "heavy" her entire life. Her medical history includes well-controlled HTN and hyperlipidemia. On physical examination, her blood pressure is 130/84 mm Hg, and her BMI is 37 kg/m^2. The remainder of the physical examination is normal. Laboratory studies include a fasting plasma glucose of 108 mg/dL and a serum TSH of 2.5 mIU/L. A goal is set for a reduction in weight of 5%–10%. Which one of the following treatments is the best advice for this patient?

- A. An exercise prescription for 30 minutes of brisk walking 5 or more times a week, progressing to 45–60 minutes of vigorous exercise on most days.
- B. Orlistat, 120 mg with meals, plus a calorie-restricted diet with a calorie deficit of 500 kcal/day, < 30% calories from fat, and limited refined sugars.
- C. Pioglitazone 45 mg/day, plus a protein-rich, carbohydrate-restricted diet.
- D. A calorie-restricted diet with a calorie deficit of 500 kcal/day, <30% of calories from fat, limited refined sugars, combined with a progressive exercise program.

Workbook Page 1-199; Answer: Page 1-214.

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Workbook Page 1-199; Answer: Page 1-214.

Adrenal Disease - Clinical Pearls

- When the patient LOOKS GREAT (tanned) but FEELS AWFUL, think Addison's disease.
- Most people who look like they have Cushing's syndrome do not have it.
- Physiological daily cortisol production rates vary between 5 and 10 mg/m2, which is equivalent to the oral administration of 15 to 25 mg hydrocortisone, *i.e.* cortisol.
- A physiologic dose of GCs is about 5–7.5 mg of prednisone (or its equivalent) per day.
- The 5 S's of adrenal crisis management are salt, sugar, steroids, support, and search (for the underlying cause).

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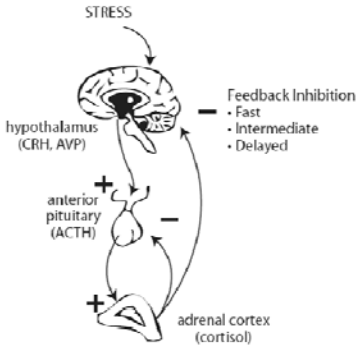
Hypothalamus-Pituitary-Adrenal Axis



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Addison's Disease - Classification

- Primary
  - Addison's disease (autoimmune cause accounts for 70%–90% of all cases of primary disease)
  - Deficiency in all adrenal steroids; mineralocorticoid replacement often necessary
- Secondary
  - Abrupt discontinuation of exogenous corticosteroid therapy (though can still occur more than one year after GC taper and discontinuation)
  - Pituitary disease (loss of anterior pituitary corticotrophs or disruption of the pituitary stalk)
- Tertiary
  - Hypothalamic failure

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Addison's Disease - Clinical Presentation

- Weakness
- Fatigue
- Anorexia
- Nausea
- Salt craving (primary adrenal insufficiency)
- Dizziness
- Hypotension
- Hypovolemia
- Dehydration
- Weight loss
- Decreased axillary/pubic hair (1^0 disease, especially in women; loss of adrenal androgen secretion)
- Hyperpigmentation (1^0 disease, elevated ACTH)

Page 1-200

Addison's Disease - Diagnosis

- Physical examination
  - Low blood pressure
  - Orthostasis
  - Hyperpigmentation (primary)
- Laboratory evaluation
  - Low plasma cortisol (less than 5 mcg/dL)
  - Cosyntropin stimulation test 250 mcg; cortisol >18 mcg/dL 30-60 min later rules out adrenal insufficiency; 1 mg: >18mcg/dL at 30 minutes
  - Hyperkalemia (primary, but < 50%)
  - Hyponatremia (80%)
  - Hypoglycemia

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Glucocorticoid Preparations

Table 2.

Corticosteroid	Equivalent Dose (mg)	Mineralocorticoid Activity
Cortisone	25	2+
Hydrocortisone	20	2+
Prednisone	5	1+
Methylprednisolone	4	0
Dexamethasone	0.75	0

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GC Replacement Therapy

- Adrenal crisis
  - Hydrocortisone 100 mg intravenously every 8 hours for 24 hours; then 50 mg every 6–8 hours after achieved hemodynamic stability, tapered to maintenance dose after 4–5 days.
  - Normal saline/5% dextrose: several liters
  - 5S: Steroids, salt, sugar, support, and search for underlying cause
- Typical replacement
  - Hydrocortisone 20 mg orally every morning, 10 mg orally every night
  - Fludrocortisone 0.05–0.2 mg every morning; mineralocorticoid replacement commonly required in primary disease, uncommon in secondary/tertiary disease
- Sick-day rules
  - Double or triple your GC replacement dose.
  - If you are vomiting, you must go to the emergency department.
- Monitoring
  - Symptom resolution
  - Blood pressure
  - Weight
  - Electrolytes

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GC Replacement Therapy

- Monitoring – In General
  - Signs of underreplacement (weight loss, fatigue, nausea, myalgia, lack of energy)
  - Signs of overreplacement (weight gain, central obesity, stretch marks, osteopenia/osteoporosis, impaired glucose tolerance, HTN)
  - Take a detailed account of stress-related GC dose self-adjustments since last visit; potential adverse events including emergency treatment and/or hospitalizations
  - Wear a MedicAlert bracelet
  - Check knowledge of sick-day rules and reinforce emergency guidelines involving partner/family members
  - Consider prescription of a hydrocortisone emergency self-injection kit, particularly if delayed access to acute medical care is likely (rural areas, travel)
  - Monitor use of cytochrome P450 (CYP) 3A4 inhibitors and inducers; may require glucocorticoid dose adjustment

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Case #8

- Mary Jane is a 44-year-old patient with pan-hypopituitarism. She feels rundown, is light-headed, and is running a low-grade fever. She is somewhat nauseous but she has not vomited. Which one of the following should she be counseled to do?

A. Go directly to the emergency department.
B. Double her GC replacement dose.
C. Double her T4 replacement dose.
D. Drink more water.

Workbook Page 1-202; Answer: Page 1-214.

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A. Go directly to the emergency department.
B. Double her GC replacement dose.
C. Double her T4 replacement dose.
D. Drink more water.

Workbook Page 1-202; Answer: Page 1-214.

Cushing's Syndrome - Classification

- Pituitary (Cushing's disease, 65%–75% of cases)
- Adrenal (15%–20%)
- Ectopic (10%–15%)
- Iatrogenic (most common cause)
- Also classified as:
  - Adrenocorticotropic hormone (ACTH)-dependent (e.g., pituitary tumor [Cushing disease], ectopic ACTH-secreting syndrome)
  - ACTH-independent (e.g., adrenal adenoma or carcinoma, drug induced)

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Cushing's Syndrome - Clinical Presentation

- Central obesity with moon face, buffalo hump ***
- Ecchymoses
- Facial plethora ***
- Hypertension ***
- Myopathy with or without proximal muscle weakness ***
- Striae (wide, more than 1 cm) ***
- Hirsutism (women) ***
- Neuropsychiatric symptoms (depression to mania)
- Back pain (osteoporotic fracture)
- Oligo/amenorrhea
- Acne
- Fungal infections
- Hypokalemia
- Other—Hyperglycemia, hyperlipidemia, HTN, osteoporosis, atherosclerosis

Page 1-203

Cushing's Syndrome - Diagnosis

- Document GC excess.
  - 24-hour urine free cortisol level; 24-hour urine for free cortisol and creatinine; free cortisol greater than 3 (or 4) times the ULN (upper limit of normal, 20-90 mcg per 24 hr) is diagnostic
  - 1-mg overnight dexamethasone suppression test (ONDST)
    - 1 mg of dexamethasone given orally between 11 pm and midnight and check cortisol level between 8 am and 9 am the next morning
    - Normals will suppress to less than 5 mcg/dL.
    - Very few false negatives but HIGH RATE OF FALSE-POSITIVE results (low specificity). Those who do not suppress require further follow-up for diagnosis. A normal result of the 1-mg ONDST rules out Cushing's syndrome, but an abnormal result (failure to suppress cortisol) does not necessarily confirm the diagnosis.
  - Late night salivary cortisol level (nls are assay dependent) or MN plasma cortisol (>7.5 mcg/dL)
  - Other tests (e.g., plasma ACTH) and imaging studies (e.g., pituitary MRI, adrenal CT) are then used to identify the specific source of hypercortisolism (pituitary, adrenal, ectopic).

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Cushing's Syndrome – Treatment Depends on the cause of the Cushing's

- Surgical - TOC if the tumor can be localized and there are no CIs.
  - Transsphenoidal adenomectomy: TOC for pituitary tumors (Cushing's disease)
  - Adrenalectomy: TOC for adrenal tumor; steroid replacement required postop for 6-12 months (contralateral adrenal atrophy)
  - Thoracotomy: TOC for ectopic ACTH-producing lung tumor
- Irradiation of the pituitary: 6-12 month lag time, high incidence of panhypopituitarism; typically reserved for surgical failures
- Drug induced: Taper and discontinue GC as soon as possible.
- Medication: used in
  - patients with un-localized or un-resectable tumors
  - patients who are not surgical candidates
  - patients who did not respond to or relapsed after surgery
  - May also be used in preparation of surgery

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Cushing's Syndrome – Treatment

- Medication Therapy
  - Steroidogenic inhibitors
    - Ketoconazole, Metyrapone, Aminoglutethimide, Etomidate
  - Adrenolytic agents
    - Mitotane
  - Neuromodulators of ACTH release
    - Cyproheptadine, Bromocriptine, Cabergoline, Vanillylmandelic acid, Octreotide
  - GC-receptor blocking agents
    - Mifepristone

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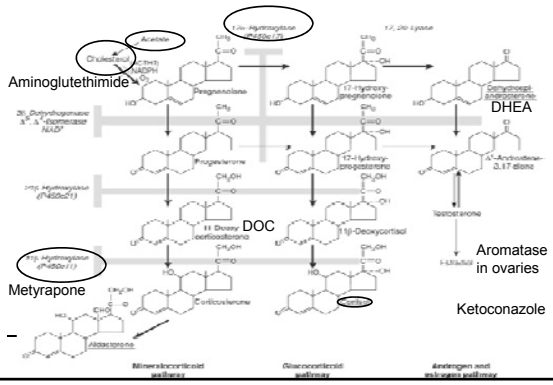
Adrenocortical Hormone Biosynthesis



Cushing's Syndrome - Medication Therapy

- **Ketoconazole** (Nizoral)
  - Mechanism of action: Inhibits cortisol production by inhibition of 11B- and 17-hydroxylase enzymes; also inhibits gonadal steroid synthesis
  - Dose
    - 400–1200 mg/day in divided doses; start at 200 mg/d and increase by 200 mg/d q2-3 days
    - Titrate to normal cortisone level or give high dose with GC replacement.
  - Adverse effects
    - Nausea
    - Hepatotoxicity
    - Gynecomastia
    - Adrenal insufficiency
  - CIs: Concomitant use with cisapride
  - Other
    - Cytochrome P450 enzyme inhibitor
    - Requires acidic gastric pH for absorption

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Cushing's Syndrome - Medication Therapy

- **Metyrapone** (Metopirone)
  - Mechanism of action: 11B-hydroxylase inhibitor (final step in cortisol synthesis); can also prevent aldosterone production
  - Dose
    - 1–4 g/day divided every 6 hours (start with 250 mg BID)
    - MUST GIVE GC replacement
  - Adverse effects
    - Nausea, vomiting, anorexia
    - Dizziness, headache, sedation
    - Hirsutism and acne (caused by excess androgen production)
    - Hypokalemia and HTN (caused by excess 11-deoxycorticosterone proximal to the blockade)
  - Other
    - DOC for pregnant woman; compassionate use only

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Cushing's Syndrome - Medication Therapy

- **Aminoglutethimide** (Cytadren)
  - Mechanism of action: Blocks the conversion of cholesterol to pregnenolone, thereby inhibiting the synthesis of all steroid-derived hormones; up to 50% reduction in cortisol levels
  - Dose
    - 500–2000 mg/day divided every 6–12 hours
    - GC replacement is required
    - Often used with metyrapone in pituitary Cushing's (is more effective and results in fewer side effects)
  - Adverse effects
    - Anorexia, nausea, vomiting
    - Lethargy, drowsiness, dizziness
    - Hepatotoxicity
    - Rash
  - Other
    - Decrease anticoagulant effect of warfarin
    - Increase metabolism of exogenous GCs

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Cushing's Syndrome - Medication Therapy

- **Mitotane** (Lysodren)
  - Mechanism of action
    - Inhibits 11B-hydroxylase and adrenal cholesterol synthesis
    - Adrenolytic agent at higher doses, causing adrenocortical atrophy
  - Dose
    - 2–12 g/day divided every 6 hours
    - **Requires replacement GC dose for life** (50% permanent hypoadrenalism if treated over 6 months; consider hospitalization prior to initiation)
  - Adverse effects
    - Anorexia, nausea, vomiting, diarrhea
    - Lethargy/somnolence
    - Rash
    - Hypercholesterolemia
  - Other
    - Available as compassionate use only

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Cushing's Syndrome - Medication Therapy

- **Etomidate**
  - Mechanism of action
    - Anesthetic, inhibits 11-hydroxylase
  - Other
    - Parenteral use only
    - Use limited to patients awaiting surgery
- **Spironolactone**
  - sometimes used to treat the HTN and hypokalemia in Cushing's syndrome

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Cushing's Syndrome - Medication Therapy

- Mifepristone (Korlym)
- Used to treat hyperglycemia associated with Cushing's disease
  - M/A: Blocks the binding of cortisol to its receptor; orphan drug, 5000 pts per year
  - SE's: Nausea, fatigue, headache, joint pain, vomiting, edema of hands/feet, dizziness, poor appetite; possible adrenal insufficiency, hypokalemia, vaginal bleeding

Hyperaldosteronism - Classification

- Bilateral adrenal hyperplasia (70% of cases)
- Aldosterone-producing adenoma (Conn's syndrome, 30%)
- Adrenal carcinoma (rare)
- Licorice ingestion
- Pseudohyperaldosteronism—Liddle's syndrome (very rare); treat with amiloride

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Hyperaldosteronism - Clinical Presentation

- Consider in patients with difficult-to-control HTN and hypokalemia
- Most commonly diagnosed in 30- to 50-year-olds
- Weakness
- Muscle cramping
- Paresthesias
- Headache
- Fluid retention
- Polyuria (nocturnal), polydipsia
- Hypertension
- Laboratory findings: hypokalemia, hypernatremia, hyperglycemia, metabolic alkalosis (elevated serum bicarb)

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Hyperaldosteronism - Diagnosis

- Elevated plasma aldosterone-plasma renin activity ratio (more than 20)
- Elevated 24-hour urine for aldosterone (more than 12 mg/day)
- CT scan; adrenal venous sampling

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Hyperaldosteronism - Treatment

- Surgical—TOC for adenomas (laparoscopic resection of the adenoma)
- Medical—TOC for bilateral hyperplasia
  - Spironolactone (Aldactone)
    - Mechanism of action: Specific aldosterone antagonist
    - Dose: 25–50 mg 2 times/day to start (minimize GI adverse effects), maximal dose 400 mg/day; typical maintenance dose of 200 mg/day
    - Adverse effects
      - Gynecomastia (9%)
      - Nausea
      - Impotence (inhibits testosterone synthesis)
      - Menstrual irregularities
      - Hyperkalemia
  - Eplerenone (Inspra)
    - Mechanism of action: Specific aldosterone antagonist (with low affinity for androgen and progesterone receptors)
    - Dose: 50 mg/day; may increase to 2 times/day
    - Adverse effects
      - Gynecomastia (1%)
      - Hyperkalemia

Male Hypogonadism - Clinical Presentation

- Decreased sexual desire
- Erectile dysfunction
- Loss of energy/fatigue
- Depression
- Loss of muscle mass with increased percentage of body fat
- Osteoporosis

Male Hypogonadism - Diagnosis

- Diagnosis should only be sought in men with signs and symptoms and low T levels (less than 300 ng/dL).
- Morning total T levels for initial testing and confirmation
- Free T (less than 5 ng/dL) used if total T is low normal and altered SHBG levels are suspected
- Diagnosis should not be made during acute illness.
- General screening not recommended but consider in certain situations (infertility, low trauma fracture in young man)

Male Hypogonadism - Treatment

- Oral androgens (1930s)
  - 17-α alkylation: Examples
    - Methyltestosterone
    - Fluoxymesterone: Hepatotoxic. Because of this adverse effect, oral T replacement products should not be used.
  - 17β esterification (not available in the United States)
- T esters (1950s)
  - T enanthate (Delatestryl)
  - T cypionate (depot T)
  - Administered as a deep intramuscular injection; 200–400 mg every 2–4 weeks; results in high peaks (fluid retention, polycythemia) and low trough (recurrence of symptoms) levels of T (T crash). Measure mid-interval levels
  - Represents approximately 20% of T replacement therapy (TRT)
- Transdermal scrotal patches (1980s)
  - Good absorption and physiologic T levels but requires shaving of scrotal skin; apply daily.
    - Testoderm - 4 and 6 mg patches

Male Hypogonadism - Treatment

- Transdermal non-scrotal patches (1990s)
  - Physiologic levels of T but skin irritation (about one-third) and limited flexibility in dosing; measure T levels 3-12 hours after patch placed
  - Apply one patch (2.5–7.5 mg/day) nightly.
    - Androderm—Apply to abdomen, lower back, thigh, or upper arm; 2.5 and 5 mg patches (being replaced by smaller 2 and 4 mg patches)
    - Testoderm TTS—Apply to arm, back, or upper buttocks; 2.5 and 5 mg patches
- T gels (2000s)
  - Allow to dry on skin before dressing; apply at least 2-6 hours before showering or swimming; most popular T replacement products (70% of TRT)
  - Hydroalcoholic 1% or 2% T gel
  - Physiologic levels of T
  - Precautions to prevent transference to partner and exposure to children
  - 5–10 mg applied once daily, preferably in the morning
    - AndroGel—Apply to upper arms, shoulders or abdomen; 2.5 and 5 gm gel packets and metered-dose pump (1.25 gm per actuation, 60 pumps; twin pump package)
    - AndroGel 1.62%—1.25 gm of gel (20.25 mg of T) per pump; start at 2 pumps applied to shoulders or upper arms each morning
    - Testim—Apply to upper arms and/or shoulders; 5 gm T gel tubes, packages of 30
    - Fortesta—Apply to front or inner thighs; metered-dose pump; 2% T gel

Male Hypogonadism - Treatment

- Buccal T (2003)
  - Mucoadhesive tablet that provides controlled release of T through the buccal mucosa
  - Avoids first-pass metabolism
  - Gum irritation (9%), gum tenderness (6%), bitter taste (4%)
  - 30 mg applied to the upper gum twice daily
    - Striant
- Implantable T pellets (2005)
  - Each pellet contains 75 mg of crystalline T.
  - Pellets slowly release T over months.
  - 150–450 mg implanted subcutaneously every 3–6 months
    - Testopel
- T solution (2010)
  - Hydroalcoholic 2% T solution
  - Physiologic levels of T
  - Precautions to prevent transference to partner (though less likely with these preparations than gels)
  - Applied once daily, preferably in the morning; 60 mg (2 pumps), apply to underarm; topical solution; metered-dose application (30 mg/1.5 cc); 60 pumps per 90 cc bottle; patients who use antiperspirant or deodorant should apply it before using T to avoid contamination of the deodorant
    - Axiron

Testosterone- Adverse Effects

- Edema
- Acne
- Gynecomastia (aromatization of T to estradiol)
- Polycythemia
- Dyslipidemia
- Worsened sleep apnea
- Increased BP
- Hair loss/balding (increased production of dihydrotestosterone from T)
- Infertility (high doses decrease spermatogenesis)
- Site reactions

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Testosterone- Contraindications

- History of breast or prostate cancer
- Enlarged prostate or palpable nodule, or prostate-specific antigen greater than 3 ng/mL
- Severe untreated benign prostatic hyperplasia
- Erythrocytosis (hematocrit > 50%)
- Untreated obstructive sleep apnea
- Severe, uncontrolled heart failure
- Pregnancy/Breast feeding

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Male Hypogonadism - T Response/Monitoring

- Response
  - 1 month: improved libido, spontaneous erections, and sexual activity
  - 3 months: increased muscle mass and decreased fat
  - 6 months: improved BMD
- Monitoring
  - Baseline: symptoms, BP, prostate exam and labs
  - Follow-up:
    - Symptoms: energy, libido, spontaneous erections, sexual activity, mood, BPH symptoms
    - Labs: total T, free T, DHT, SHBG and Estradiol levels, hematocrit, PSA at 1 and 3 months then annually; LFT's and cholesterol profile annually; DXA after 1-2 years
    - Physical Examination: BP, rectal exam, observe for acne, gynecomastia, hair loss, edema

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