DIABETES MELLITUS

Raed Abughazaleh, PharmD, BCPS
PHAR 551: Pharmacotherapy I
Birzeit University

Diabetes Mellitus

- A group of chronic metabolic disorders associated with hyperglycemia
- DM is leading contributor to ESRD, non-traumatic limb amputations, blindness
- Approx 2/3rd of pts with DM die of a CV event
- 7th leading cause of death in the U.S.
- Up to 20% of DM is undiagnosed
- Type 1 DM ~ 10% of total DM

Diabetes Mellitus

- Rising prevalence of Type 2 DM in West Bank
  - 9.7% (2000), 15.3 (2010), 20.8 (2020), 23.4 (2030)*
- Causes for increased prevalence of T2DM
  - Obesity
    - Overweight : 58%
    - Obese (M/F)*: 22.1/37.2 % (2000), 29.1/39.6 % (2010)
  - Physical inactivity (~75% of people do not engage in any vigorous physical activity)
  - Ageing population

*Abu Rmeileh NME, Husseini A, Capewell S, *et al*. Preventing type 2 diabetes among Palestinians: comparing five future policy scenarios. *BMJ Open* 2014;3:e003558.

Classification of Diabetes

- Type 1 Diabetes Mellitus
  - Autoimmune destruction of β-cells
    - Antibodies to insulin, islet cells, glutamic acid decarboxylase
    - In rare cases idiopathic
  - Absolute insulin deficiency
  - Diagnosed before age 30, but possible at any age
    - 50-60% diagnosed before the age of 16-18 yrs
    - At older age → latent autoimmune diabetes in adults (Type 1.5 DM)
  - Typically presents with DKA, especially in younger pts

Classification of Diabetes

- Type 2 Diabetes Mellitus
  - Slow and progressive
  - Combination of diminished release of insulin, increased resistance, and other hormonal irregularities
  - Often preceded by pre-diabetes
    - IFG: 100-125 mg/dL
    - IGT: post-prandial 140-199 mg/dL
    - A1c: 5.7-6.4%
  - Majority of pts with T2DM are obese, with an increasing percentage in obese children

Classification of Diabetes

- Type 2 Diabetes/Cont.
  - Risk factors: first-degree family history (parent or sibling), obesity, inactivity, race/ethnicity, pre-diabetes state, HTN, HDL < 35, TG > 250, hx gestational diabetes, hx delivering large baby (> 4kg), etc.
- Gestational Diabetes Mellitus
  - Glucose intolerance during pregnancy
  - 2-10% incidence in pregnant women
  - Women with GDM have 35-60% chance of developing T2DM later on

Classification of Diabetes

- Gestational Diabetes/Cont.
  - All pregnant mothers should be screened between 24-28 wks gestation
  - Good management of GDM reduces perinatal morbidity and mortality
- Other causes for diabetes
  - Genetic defects in various components of blood sugar control
  - Cystic fibrosis
  - Medications (glucocorticoids, clozapine, etc.)

Pathophysiology

- Normally fasting BS is maintained between 79-99 mg/dL by insulin and glucagon (and other factors like growth factors, epi, cortisol)
  - Glucagon
    - Secreted by α-cells in the islets
    - Secreted in fasting state, stimulates liver glycogenolysis
  - Insulin
    - Secreted by β-cells in the islets
    - Secreted in the fed state, lowers serum glucose levels via increasing cellular uptake, suppressing hepatic glucose production

Pathophysiology

- In Type T2DM → impaired insulin secretion, increased insulin resistance, elevated glucagon
- Impaired insulin secretion
  - Burnout of β-cells 2/2 insulin resistance
  - Hyperinsulinemia leading eventually to hypoinsulinemia
- Insulin resistance
  - Often present for many years before diagnosis
  - Highly associated with metabolic syndrome
    - Abdominal obesity, ↑ TG, ↓ HDL, HTN, ↑ FBS

Pathophysiology

- Insulin resistance/Cont.
  - Occurs in the following tissues:
    - Liver: fasting hyperglycemia is due to increased hepatic glucose production
    - Muscles: 85% of glucose uptake occurs in muscle tissue
    - Adipocytes: insulin is potent inhibitor of lipolysis
- Impaired glucagon secretion (excessive)
  - Most pts with 10-20 yr hx T1DM lose ability to secrete glucagon
  - Up-regulated in pts with T2DM
  - Leads to excess hepatic glucose production

Pathophysiology

- Incretin Effect
  - Hormones found in gut that affect insulin release
  - Glucagon-Like Peptide -1 (GLP-1) and Glucose-dependent Insulinotropic Peptide (GIP)
  - Incretins: increase insulin release, suppress glucagon release, slow gastric emptying, increase satiety
  - Food ingestion → Incretin secretion → Insulin secretion and glucagon suppression → Incretin breakdown with DPP-4

Clinical Presentation

Characteristic	Type 1 DM	Type 2 DM
Usual Onset Age	Childhood/adolescence	Adult
Speed of onset	Abrupt	Gradual
Body type	Thin	Obese or history of
Metabolic synd.	No	Often
Autoantibodies	Present	Not present
Symptoms	Symptomatic	Often asymptomatic
Ketones at diagnosis	Present	Rare
Acute complications	DKA	Hyperosmolar hyperglycemic state
Need for insulin	Immediate	Years after diagnosis

Adapted from Dipiro's *Pharmacotherapy: Principles and Practice* 3rd Ed; and from Dipiro's *Pharmacotherapy: A Pathophysiologic Approach* 8th Ed

Clinical Presentation

- 20-40% of pts with Type 1 DM will present with DKA after several days of polyuria, polydipsia, polyphagia, wt loss
- Type 1 DM pts may enter "honeymoon" phase
  - BS easily controlled with small amounts of insulin
- Type 2 DM typically asymptomatic on diagnosis
  - Occasionally lethargy, polyuria, nocturia, polydipsia seen
  - Significant wt loss not common

Diagnosis

- Used to be based on plasma glucose criteria (FPG, OGTT)
- In 2009, international consensus reached to use A1C as preferred diagnostic criteria when available
  - Advantages
    - Greater convenience (fasting not required)
    - Unaffected by day-to-day fluctuations
  - Disadvantages
    - Availability
    - Cost
    - Inaccurate correlation to avg BS in some individuals
    - Possible varying rates of glycation amongst different races
    - Lack of validation in children

Diagnosis
ADA's Criteria for Diagnosis of Diabetes

- A1C ≥ 6.5 %
- *OR* FPG ≥ 126 mg/dL
  - Fasting: no caloric intake ≥ 8h
- *OR* 2-h plasma glucose ≥ 200 mg/dL during OGTT (75 g anhydrous glucose dissolved in water)
- *OR* a random plasma glucose ≥ 200 mg/dL in pts with classic symptoms of hyperglycemia or hyperglycemic crisis

Diagnosis
Gestational Diabetes

- OGTT is recommended during 24-28 week gestation period
- Diagnosis is made if any of the following fasting BS criteria is met:
  - Fasting: ≥ 92 mg/dL
  - 1 h: ≥ 180 mg/dL
  - 2 h: ≥ 153 mg/dL

Prevention of Type 2 Diabetes

- High risk individuals can significantly decrease rate of DM onset
- Intensive lifestyle modification
  - e.g., ~58% reduction after 3 years in one study, ~43% reduction at 20 years in another study
  - Lifestyle modifications
    - 7% wt reduction
    - Moderate physical activity of at least 150 min/wk
- Medications for prevention
  - Metformin
    - Strong evidence base and long-term safety
    - Additional factors that favor efficacy: BMI > 35 kg/m^2, Age < 60, women with prior GDM
  - Other drugs: no strong efficacy/safety base

Medical Workup and Monitoring

- BP: every visit
- Dilated eye exam- initially then yearly
- Foot exam: every visit
- A1C: every 3 mo till at goal, then every 6 mo
- If not performed within the past year:
  - Fasting lipid profile: at least yearly
  - LFTs
  - Spot urine-to-albumin ratio
  - SCr
  - TSH if Type 1 DM

Treatment
Goals of Therapy

- Primary goal: glycemic control
  - A1C ~7% or lower for majority of population
  - A1C target of < 6.5 in select populations
  - A1C target of < 8% in select populations
- Secondary goals:
  - Preserving residual β-cell function
  - Preventing acute and chronic complications
  - Slow down microvascular and macrovascular damage

Glucose Monitoring

- Self-Monitored Blood Glucose (SMBG)
  - Standard method for routine monitoring
  - Useful for optimizing safety and efficacy of meds
  - Should be done at least TID for pts on multiple-dose insulin or insulin pump
  - Continuous glucose monitoring (CGM)
    - SQ sensor (interstitial fluid sampling)
    - Needs to be calibrated regularly with blood sample
- HbA1c
  - Hb lifespan = 3 mo
  - eAG (mg/dL) = (28.7 x A1c) – 46.7
  - A1C of 7% → eAG of 154 mg/dL

General Approach to Treatment
Type 1 Diabetes

- Most people with Type 1 DM should be treated with MDI injections (3-4/d) of basal and prandial, or continuous SQ insulin infusion (pump) (EL-A)
- Most people with Type 1 DM should be educated on how to adjust prandial insulin dose based on pre-meal BG, expected calorie load, and anticipated activity
- Most pts with Type 1 DM should use insulin analogs to minimize risk for hypoglycemia (EL-A)

General Approach to Treatment
Type 2 Diabetes

- Patient-centered approach is advocated
  - Effects on weight, comorbidities, hypoglycemia risk, patient preference, cost, efficacy, adverse effects, life expectancy, etc.
- Metformin is the preferred initial pharmacological agent for Type 2 DM (EL-A)
- Insulin therapy should be considered in newly diagnosed Type 2 DM patients with markedly symptomatic and/or elevated BG or A1C

General Approach to Treatment
Type 2 Diabetes

- If non-insulin regimen reaches max tolerated doses without achieving A1C goal over 3 months then you should add another oral agent or a glucagon-like peptide 1 (GLP-1) receptor agonist or insulin (basal or MDI)
- Insulin therapy is eventually indicated for many pts with Type 2 DM

General Approach to Treatment
Gestational Diabetes

- Poorly controlled BG in pregnancy causes:
  - Abnormally large fetus
  - Risk for hypoglycemia upon birth
- Diet control and exercise should be tried first
  - Diet should be balanced to provide adequate intake for development of fetus
- Insulin is primary therapy for hyperglycemia in pregnant women with uncontrolled BG
  - Category B: detemir, aspart, lispro, regular insulin
- Some oral agents shown safe in small studies but should be avoided

Non-Pharmacologic Therapy

- Medical Nutrition Therapy
  - For all pts with pre-diabetes, T1DM, and T2DM
  - If available should be individualized by dietitian
  - Reduction of energy intake while maintaining healthful eating pattern
  - No ideal percentage of calories from carbs, proteins, fats for all pts → should be individualized
  - Calorie counting/monitoring is recommended
  - Fat quality is far more important than quantity
- Physical Activity
  - At least 150 min/wk of moderate-intense aerobic physical activity (50-70% of max HR) over ≥ 3 d/wk
  - Resistance training at least 2x/wk

Non-Pharmacologic Therapy

- Hypoglycemia
  - Any form of carbohydrate that contains glucose is preferred as treatment in the conscious pt
  - May repeat after 15 min if SMBG indicates continued hypoglycemia
  - Once resolved, pt should consume a meal or snack to prevent recurrence
  - Glucagon should be prescribed to pts at significant risk for severe hypoglycemia
- Surgery
  - Bariatric surgery may be considered for adults with BMI > 35 kg/m^2 and T2DM

Non-Pharmacologic Therapy

- Immunizations
  - Flu vaccine annually to all pts with DM who are ≥ 6 mo of age
  - Pneumococcal vaccine to all diabetic pts ≥ 2 yrs of age, one time revaccination for pts > 65 yrs if it has been longer than 5 yrs since last vaccination

Pharmacologic Therapy
Biguanides

- Metformin
- Enhances insulin sensitivity in liver and peripheral tissue, no direct effect on β-cells
  - Hypoglycemia not a concern
- Significant reduction in all-cause mortality in overweight pts with T2DM Vs. insulin or SU monotherapy
- Average reduction in HbA1C: 1.5-2%
- Able to reduce FPG in glucose toxicity (> 300 mg/dL)

Pharmacologic Therapy
Biguanides

- Reduces TG and LDL, increases HDL
- Modest reduction in wt (2-3 kg)
- Reduces macrovascular complications
  - Stroke risk reduction vs. insulin or SU
  - Reduction in DM-related MI vs. standard treatment
- GI side effects common (discomfort, anorexia, stomach fullness, diarrhea)
  - Minimize by slow titration and giving with meals
  - Often transient

Pharmacologic Therapy
Biguanides

- Lactic acidosis
  - Rare but life-threatening
  - Highest risk with age and renal dysfunction
  - Manufacturer C/I: Cr 1.4 mg/dL in women, 1.5 mg/dL in men, or CrCl < 60 mL/min in men/women
  - Alternate recommendation (NICE guidelines):
    - CrCl ≥ 45 to < 60, continue use, monitor renal fcn every 3-6 mo
    - CrCl ≥30 to < 45, continue with caution in pts currently on metformin, consider reducing dose by 50%, monitor renal fcn every 3 mo, do not initiate in pts
    - CrCl < 30, discontinue use in all pts

Pharmacologic Therapy
Biguanides

- Hold therapy for pts at increased risk for receiving nephrotoxic dye (surgery, hospitalization, etc.)
  - Hold on day of therapy, resume after 48h if normal CrCl
- Avoid initiating in pts > 80 y/o
- Dosing (metformin)
  - Initial: 500 mg BID with meals
  - May increase by 500 mg/d weekly until glycemic goal achieved or max dose of 2000 mg/d reached
  - ER formulation available as QD

Pharmacologic Therapy
Sulfonylureas

- First generation (e.g., chlorpropamide) vs. second generation (e.g., glimepiride, glipizide, glyburide)
- Enhance insulin secretion by binding to Sulfonylurea Receptors (SUR) on β-cells
  - Glucose-insensitive release of insulin
- Inhibit liver glucose production
- Increases insulin sensitivity in peripheral tissue
- All are metabolized and cleared renally → should be used cautiously
- All SUs are equally effective at equipotent doses

Pharmacologic Therapy
Sulfonylureas

- Average reduction in HbA1C: 1.5-2%
- Not effective in glucose toxicity
- Reduces microvascular complications
- No reduction shown in macrovascular complications
- AEs: hypoglycemia, weight gain, displacement of protein binding (first gen.)

Pharmacologic Therapy
Sulfonylureas

- Dosing:
  - Start with low dose for elderly and pts with renal dysfunction
  - Titrate dose every 1-2 wks to desired effect or max dose
  - Glipizide
    - 5-20 mg QD (IR given in BID if > 15 mg/d)
    - Take 30 min before meals
    - Start at 2.5 mg/d for elderly

Pharmacologic Therapy
Non-Sulfonylurea Secretagogues

- AKA meglitinides
  - Repaglinide, nateglinide
- Rapid insulin secretagogues via binding to a receptor on β-cells adjacent to SUR
  - Quick onset, short half life
- Increase insulin secretion during meals
- Max A1C reduction ~ 1%
- Should not combine with SUs (no added benefit)
- Given TID within 30 min prior to meals
- AEs: hypoglycemia, weight gain

Pharmacologic Therapy
Thiazolidinediones (TZDs)

- Rosiglitazone (Avandia), pioglitazone (Actos)
- Indirectly increase insulin sensitivity in muscle and liver tissue
  - PPAR-γ agonists in fat and vascular cells
- Average reduction in HbA1c: 1.5%
- Max efficacy may take 3-4 mo of therapy
  - Important for pt education/compliance
- Both agents can increase HDL, LDL, with mixed effect on TG

Pharmacologic Therapy
Thiazolidinediones (TZDs)

- AEs:
  - Edema and fluid retention:
    - Dose-related
    - Edema in ~5% of pts on it
    - C/I in pts with symptomatic HF
    - Black Box Warning: may cause or exacerbate HF
  - Hepatotoxicity
    - Reversible upon D/C of drug
    - Check LFTs at baseline and periodically

Pharmacologic Therapy
Thiazolidinediones (TZDs)

- AEs/Cont:
  - Weight gain
    - Average 1.5-4 kg gain
    - Dose-related 2/2 fluid retention, fat accumulation, and increased appetite
  - Fractures
    - Increased risk for upper and lower limb non-osteoporotic fxs (wrists, forearms, ankles, feet..)
    - Baseline fx risk should be evaluated when considering therapy

Pharmacologic Therapy
Thiazolidinediones (TZDs)

- AEs/Cont:
  - May increase risk for bladder cancer
    - Should be avoided in such pts
  - Rosiglitazone was thought to increase risk for AMI, however FDA has withdrawn warning 2/2 new data
- Dosing:
  - Pioglitazone: 15-45 mg QD
  - Titrate every 12 weeks

Pharmacologic Therapy
α-Glucosidase Inhibitors

- Acarbose and miglitol
- Inhibit intestinal breakdown of sucrose and complex carbs, reducing post-prandial BG
- Average reduction in HbA1c: 0.3-1%
  - 40-50 mg/dL reduction in post-prandial BG
  - Little effect on fasting BG
- AEs:
  - GI (common, limiting to use): flatulance, discomfort, bloating, diarrhea
- Dosing: given with the first bite of meal 1-3x/d

Pharmacologic Therapy
Bile Acid Sequestrants

- Colesevelam
- Binds bile acids in intestinal lumen and prevents reabsorption
- Average HbA1c reduction: 0.4%
- Reduces LDL
- Weight neutral
- AEs: contipation
- Can inhibit absorption of some drugs and ADEK vitamins
  - Should be given at least 4h prior to colesevelam

Pharmacologic Therapy
Dopamine Agonists

- Bromocriptine
- Mechanism unclear
- Average HbA1c reduction: 0.1-0.4%
- AEs:
  - nausea, rhinitis, dizziness, headache, constipation
  - D/C rate ~ 24% because of AEs

Pharmacologic Therapy
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- Sitagliptin (Januvia), saxagliptin (Onglyza), vildagliptin, alogliptin, linagliptin
- Block breakdown of GLP-1
- Effect is primarily on postprandial BG
- Average reduction in HbA1c: 0.7-1%
  - Higher reduction seen in higher A1c baseline
- No significant effect on satiety or gastric emptying → weight neutral or slight reduction
- May be administered without regard to meals

Pharmacologic Therapy
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- AEs:
  - Hypoglycemia if combined with insulin or secretagogues
  - Pancreatitis reported with all DPP-4 inhibitors
  - Increased rate of hospitalization for HF with saxagliptin (NEJM report)- under review by FDA
- Dosing
  - Sitagliptin: 100 mg QD
  - All need renal adjustment except linagliptin

Pharmacologic Therapy
Insulin

- Anabolic and anticatabolic hormone
  - Plays major role in protein, carb, fat metabolism
- Proinsulin → Insulin + C-peptide
- No max dose → titrated to effect
- Insulin analogs:
  - Modified to impart specific PK advantages
  - AA changes that speed up dissociation from dimers to monomoers (lispro, glulisine, aspart), changes in isoelectric point (glargine), attaching fatty acid moiety (detemir)
  - Combining with zinc and protamine

Pharmacologic Therapy
Insulin

- All DM injectables made with human rDNA
- SQ absorption depends on:
  - Solubility
  - Insulin concentration
  - Additives (protamine, Zinc, etc.)
  - Blood flow to area (rubbing of site, skin temp..)
  - Injection site

Pharmacologic Therapy
Insulin

- Regular or NPH insulin absorption is affected by inj. site, while insulin analogs are not
  - (most rapid to slowest): abdominal fat, posterior upper arms, lateral thigh, superior buttocks area
- Insulin is degraded in liver (20-50%), muscle, kidney (15-20%)
  - May accumulate in renal failure

Pharmacologic Therapy
Bolus Insulins

- Regular insulin (short-acting)
  - Natural or human insulin
  - Unmodified crystalline
  - Clear solution, forms hexamers in SQ, dissociates into dimers then monomoers before absorption
  - PK:
    - Onset: 30-60 min
    - Peak: 2-3 h
    - Duration: 3-6 h
  - Mealtime coverage, give 30 min prior to meal
  - Only insulin that can be given IV ($t_{1/2}$ = 9 min)

Pharmacologic Therapy
Bolus Insulins

- Regular Insulin (short-acting)/Cont:
  - U-100 Vs. U-500 (Regular insulin only)
    - Compared to U-100, U-500 has increased duration of action
- Rapid-acting insulin
  - Glulisine, aspart, lispro
  - Manipulation of AAs in regular insulin alters PK
  - PK:
    - Onset: 15-30 min
    - Peak: ~0.5-3h depending on agent
    - Duration: 3-5h
  - Dosed before or with meals

Pharmacologic Therapy
Basal Insulins: Intermediate

- Intermediate-duration insulin
- NPH: (neutral protamine Hagedorn)
  - Protamine conjugated with regular insulin
    - Delayed onset, extended duration of action
    - Protamine may increase risk for allergic reactions
    - Poorly predictable PK
- For coverage of in-between meals and at night
  - Less popular with advent of long-acting insulin
  - Ideal for combining with short-acting insulin
  - May be mixed with aspart or lispro
  - Given BID or at bedtime

Pharmacologic Therapy
Basal Insulins: Intermediate

- PK
  - Onset: 2-4 h
  - Peak: 4-6 h
  - Duration: 8-12 h
- Suspension: should be rolled gently at least 10 times to fully re-suspend before each use

Pharmacologic Therapy
Basal Insulins: Long-Acting

- Long-Acting Insulin
- Designed for Q24h use
  - Glargine may need to be given Q12 at high doses
  - In Type 1 DM 30-60% of pts may need Q12 Detemir
- Glargine (Lantus), detemir (Levemir)
- Cannot be given IV or mixed with other insulins
- Can be given regardless of meals or time of day
- When converting to glargine, reduce dose by 20%
- PK:
  - Onset: 3-5 h
  - Duration: ~ 24 h

Pharmacologic Therapy
Combination Insulin Products

- NPH and Regular insulin
  - (NPH/Regular): Humulin 70/30; Novolin 70/30
  - Onset: 30-60 min, duration up to 16
  - Give 30 min before meals
- Protamine lispro and lispro
  - Humalog Mix 75/25
  - Onset: 15-30 min, duration 15-18 h
  - Give 10 min before meals or with meals
- Protamine aspart and aspart
  - Novolog Mix 70/30
  - Onset: 15-30 min, duration up to 24h
  - Give 10 min before meals or with meals

Pharmacologic Therapy
Insulin Pump

- 24-h basal, bolus, and supplemental insulin SQ
- Monitoring is done by pt (SMBG) or CGM
- Most commonly used in Type 1 DM
- Improves BG control, reduces fluctuations
- Regular or rapid acting insulins only
- Tubing placed SQ in abdomen
- Infusion set should be changed every 2-3d

Pharmacologic Therapy
Insulin Dosing

- Higher doses are required during acute illness
- Type 1 DM
  - Average daily requirement is 0.5-0.6 u/kg
  - Approx. 50% should be delivered as basal insulin
  - The rest should be divided over meal coverage
  - Lower doses are required during 'honeymoon phase'
  - Correction (insulin sensitivity) factor:
    - 1500 rule (regular) and 1800 rule (rapid) for in between meals

Pharmacologic Therapy
Insulin Dosing

- Type 1 DM/Cont.:
  - Insulin-to-carb ratio calculation:
    - 450 rule (regular) and 500 rule (rapid) for mealtime bolus
- Type 2 DM
  - Typically higher doses required than Type 1 DM, varying by degree of insulin resistance
  - Start by adding basal insulin to optimized oral regimen (0.1-0.2 u/kg/d). Titrate to desired effect

Pharmacologic Therapy
Insulin Dosing

- Type 2 DM/Cont.
  - If mealtime BG remain uncontrolled, pt may be started on MDI injections in addition to oral agents
  - Secretagogues may be continued after adding basal insulin, but should be stopped if MDI injections added to regimen
- Dose and agents must be individualized

Pharmacologic Therapy
Non-Insulin Injectables: GLP-1 Agonists

- Exenatide (Byetta, Bydureon), liraglutide (Victoza), albiglutide, dulaglutide
- Average A1C reduction: 01-1.9%
- Reduces post-prandial insulin secretion, suppresses glucagon production, slows gastric emptying, increases satiety
- Major advantage: good A1C reduction and significant wt. loss, low risk for hypoglycemia
  - Weight loss in majority of pts (~3 kg over 26 wks)

Pharmacologic Therapy
Non-Insulin Injectables: GLP-1 Agonists

- Not 1st line treatment, does not replace insulin
- May be combined with most oral agents and insulins (DPP-4 inhibitors??)
- Differ in $t_{½}$, mimicking of GLP-1 effects
- Exenatide:
  - IR: SQ BID within 60 min of morning and evening meals
  - ER: SQ weekly regardless of meals
  - Titrate dose monthly
- Albiglutide and Dulaglutide: weekly dosing

Pharmacologic Therapy
Non-Insulin Injectables: GLP-1 Agonists

- AEs:
  - GI: nausea, vomiting, diarrhea
  - Hypoglycemia when combined with SUs or insulin
    - SUs dose may need lowering after adding GLP-1 agonists
  - Associated with pancreatitis
    - Avoid use in pts with hx pancreatitis
  - Black Box Warning: dose- and duration-dependent thyroid tumor in animals

Pharmacologic Therapy
Non-Insulin Injectables: Amylinomimetic

- Pramlintide
- Synthetic analog of human amylin, a neurohormone co-secreted with insulin from β-cells
  - Amilyn is almost absent in Type 1 DM, and low in Type 2 DM pts requiring insulin therapy
  - Suppresses inappropriately high post-prandial glucagon levels
  - Increases satiety, slows gastric emptying, may cause weight loss by 1-2 kg

Pharmacologic Therapy
Non-Insulin Injectables: Amylinomimetic

- Average HbA1c reduction: 0.4-0.5%
- Little effect on fasting BG
- Given SQ just before meals TID
- AEs:
  - GI: nausea, vomiting, anorexia
  - Hypoglycemia:
    - Due to prandial insulin dose
    - Prandial insulin dose should be reduced by 30-50% initially

Sodium-Glucose Co-transporter Type 2 (SGLT2) Inhibitors

- Canagliflozin, dapagliflozin, empagliflozin
- Inhibit glucose reabsorption in renal tubules
- All oral QD dosing; take in the morning
- Shown to reduce FPG, systolic BP, weight
- Average A1C reduction: 0.5-1%
- Average SBP reduction: 5 mmHg
- Up to 2.5 kg weight reduction
- Low risk for hypoglycemia
  - Except if combined with insulin/secretagogues

Sodium-Glucose Co-transporter Type 2 (SGLT2) Inhibitors

- All require renal dose adjustment
- Canagliflozin increases digoxin levels
- Adverse events:
  - Related to osmotic diuresis (HoTN, dizziness..)
  - Increased UTIs and genital mycotic infections
  - Dose-related hyperkalemia (canagliflozin)
  - Increased LDL

Inhaled Insulin (Afrezza)

- Recombinant Insulin inhaled powder (4u, 8u)
- Indicated for type 1 and type 2 DM
- PD properties similar to SQ insulin lispro
  - Peak ~ 53 min
  - Duration ~ 160 min
- C/I in chronic lung disease
- Spirometry (FEV_1) required at baseline
  - Not recommended in smokers or recent quitters
- Adverse events: hypoglycemia, bronchospasms

Afrezza Dosing

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of **4 unit** (blue) cartridges needed		# of **8 unit** (green) cartridges needed
up to **4** units	**4** units	1		
5-8 units	**8** units			1
9-12 units	**12** units	1	+	1
13-16 units	**16** units			2
17-20 units	**20** units	1	+	2
21-24 units	**24** units			3

Treatment of Acute Complications
Hypoglycemia

- Clinically defined as BG < 50 mg/dL
  - Baseline BG alters hypoglycemia point
- S/S
  - Tachycardia, shakiness, sweating, fatigue, hunger, HA, AMS
- Common causes in DM
  - Missed meals while on secretagogues or insulin
  - High insulin oral or secretagogue doses

Treatment of Acute Complications
Hypoglycemia

- Treatment is indicated when pt symptomatic and BG lower than normal for that pt
- Oral Rx: 15-30 g carb (or any source of glucose), repeat in 15 min if not sufficient, consume full meal after hypoglycemia corrected
- Injectable Rx: Glucagon IM/SQ (discussed earlier)

Treatment of Acute Complications
Diabetic Ketoacidosis (DKA)

- Starvation from lack of insulin production
- Quick onset, potentially life-threatening
- Most common in young pts with Type 1 DM
- Precipitating factors
  - Infections
  - Missing insulin doses/under-dosing
  - New diagnosis

Treatment of Acute Complications
Diabetic Ketoacidosis (DKA)

- S/S:
  - Fruity or acetone breath, N/V, dehydration, polydipsia, polyuria, hyperventilation, hyperglycemia (> 250 mg/dL), ketosis and anion gap, acidosis (pH < 7.3), electrolyte abnormalities
- Severity related to acidosis degree and mental status rather than hyperglycemia degree

Treatment of Acute Complications
Diabetic Ketoacidosis (DKA)

- Treatment:
  - Hydration with NS AND IV insulin infusion to goal BG 150-250 mg/dL
  - Switch to D5 ½NS when BG < 250 mg/dL
  - Continue until ketoacidosis resolves
  - Initiate SQ insulin and wean off IV insulin

Treatment of Acute Complications
Hyperosmolar Hyperglycemic State (HHS)

- Severe hyperglycemia minus ketoacidosis
- Severe hyperosmolar and dehydrated state for several days to weeks
- Life threatening
- Most common in elderly pts with Type 2 DM
- BG > 600 mg/dL and osmolality > 320 mOsm/kg
- Treatment:
  - Rehydration, electrolyte correction, insulin infusion
  - BG corrected slowly to avoid cerebral edema

Treatment of Long-Term Complications

- Retinopathy
  - Glycemic control and optimal BP control are most proven methods to slow progression
- Neuropathy
  - Mostly affects feet (pain, tingling, numbness)
  - Commonly used agents: pregabalin, gabapentin, TCAs, duloxetine, venlafaxine, capcasin, etc.
  - Autonomic neuropathy → gastroparesis, tachycardia, impotence, constipation, orthostatic hypotention, etc.

Treatment of Long-Term Complications

- Foot Ulcers
  - 2/2 neuropathies and ischemia from PVD and foot deformities from motor neuropathy
  - Smoking cessation is key intervention
  - Glycemic control, preventing foot injuries/ infections, etc.
- Microalbumineria and Nephropathy
  - BP and BG control to slow progression
  - ACEIs, ARBs to slow progression in all DM pts regardless of HTN, titrate to max tolerated dose

Insulin in Hospitalized Patients

- Critically ill:
  - Intensive (80-108 mg/dL) Vs. < Conventional (180 mg/dL)
  - Increased risk of death in intensive group
  - Increased rate of hypoglycemia in intensive group
  - Recommended
    - Start insulin: > 180 mg/dL
    - Target BG: 140-180 mg/dL
  - Type of insulin: IV preferred over SQ

Insulin in Hospitalized Patients

- Non-critically ill:
  - Fasting goal < 140 mg/dL, random goal < 180 mg/dL
- SQ forms preferred
  - Sliding-scale rapid insulin commonly used
- When converting IV to SQ insulin dose reduction by 20-30% is advised