Diabetes Mellitus

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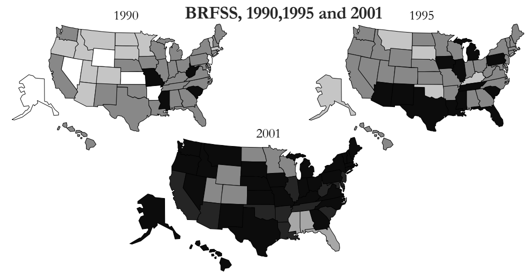


Source: Mokdad et al., *Diabetes Care* 2000;23:1278-83; *J Am Med Assoc* 2001;286:10.

Diabetes Mellitus Overview

- U.S. - 18 million (13 million diagnosed)
  - Males: 42% Females: 58%
  - Age < 18: 80,000 Age > 65: 3.2 million
- Medical Costs
  - Direct: $92 billion
    - Inpatient care (44%)
    - Nursing home (15%)
    - Office visits (10%)
  - Indirect: $40 billion

Classification

- Type 1-also known as Insulin Dependent Diabetes Mellitus (IDDM), juvenile onset, or ketosis prone
- Type 2-also known as Non-Insulin Dependent Diabetes Mellitus (NIDDM), adult onset, or ketosis resistant

Classification (cont'd)

- Impaired Fasting Glucose (IFG)-also known as chemical, latent, borderline or subclinical DM (30-60%→type 2)
- Gestational Diabetes(GDM)-glucose intolerance during pregnancy due to placental secretion of anti-insulin substance
- Secondary-due to pancreatic disease, drugs, hormones or genetic diseases

Diagnosis
Pre-Diabetes or Impaired Glucose Tolerance (IGT)

- Individuals that meet the criteria below are considered to have impaired glucose homeostasis
  - 1. FPG: 100mg/dl *to* 125mg/dl
  - 2. OGTT: 140mg/dl *to* 199mg/dl (2 hr sample)

Diagnosis-DM

- DM can be dx in any of the 3 ways
  (confirmed on a different day by any of the 3 tests)
  - 1. A FPG of $\geq$ 126mg/dl
  - 2. A random plasma glucose $\geq$ 200mg/dl with the classic symptoms: polyuria, polydipsia and unexplained weight loss (type 1)
  - 3. An oral glucose tolerance test (OGTT) value of $\geq$200mg/dl (2 hr sample)
- Patients may experience additional S/S such as fatigue, polyphagia or ↑ susceptibility to infection.
- S/S may be abrupt (type 1), gradual (type 1 or 2) or absent (type 2)

Differences between Type 1 and Type 2 DM

Characteristic	Type 1	Type 2
% of Diabetics	5-10%	90-95%
Age of Onset	> 6mos, < 30 yrs	> 40 yrs
Family History	Weak to moderate	Strong
Precipitating Factors	Autoimmune ?, viruses ?, genetic ?	Obesity
Ketosis/acidosis	Can occur	Rarely occurs
Insulin response to glucose/meals	Little or none	Delayed/impaired
Response to insulin	Usually sensitive	Often resistance
Response: diet alone	Negligible	Variable
Response: sulfonylurea	Absent	Present
Response to stress	Ketosis	Hyperglycemia
Symptoms	Polyuria, polydipsia, polyphagia, wt. Loss	Maybe asymptomatic or polyuria/dipsia

Drug-Induced Hyperglycemia

Drug	Significance	Mechanism/Comments
B-Blockers	++	↓ insulin secretion
Diazoxide	+++	↓ insulin secretion
Diuretics	++	Unknown mechanism
Glucocorticoids	+++	↑ gluconeogenesis ↓ sensitivity to insulin
Nicotinic acid	++	Unknown mechanism
Oral contraceptives	++	Unknown mechanism
Pentamidine	+++	Toxic to B-cells
Phenytoin	++	↓ insulin secretion
Sympathomimetics	++	↑glycgnolys./glucognesis
Tacrolimus	+++	Unknown mechanism

++ Clinically Significant +++ Clinically Significant w/ substantial magnitude

Goals of Therapy

Test Time	Ideal	Acceptable	Pregnant
Fasting	70-120	70-140	90-100
Preprandial	70-120	70-140	90-100
Postprandial (2hr)	< 140	150-180	100-120
HbA1c	<6.5% or <7%		

OTHER GOALS…

"Tight" vs "Loose" Blood Glucose Control

- "Tight"-attempts to normalize BG as much as possible
  - Indications: young pts, Gestational DM, absence of complications
  - Advantage: possibly fewer/delayed long-term complications
  - Disadvantages: greater risk of hypoglycemia
- "Loose"-simply attempts to prevent excessive hyperglycemia
  - Indications: presence of complications, elderly

Long-Term Complications Macrovascular Disease

- Coronary Heart Disease (CHD)
- Peripheral Vascular Disease (PVD)

- Occurs secondary to chronic hyperglycemia, altered lipid metabolism and hypertension
- The mortality rate due to macrovascular disease in Type 1 and Type 2 pts is 30% and 75% respectively
- DM pts are 2-3x more prone to MI and stroke
- Control of DM and RFs are keys to prevention

Microvascular Complications and Treatment

- Retinopathy
  - prevent by ↓ RF (smoking, hyperglycemia, hypertension) and laser photocoagulation
- Nephropathy
  - Goal: <u>Control Hypertension</u> & <u>↓ Proteinuria</u>
    - ACE Inhibitors, ARBs
    - Calcium Channel Blockers
- Neuropathy
  - Peripheral- TCAs, gabapentin, duloxetine, venlafaxine
  - Autonomic
    - Gastroparesis: metoclopramide, erythromycin
    - Diarrhea: Lomotil, loperamide, antibiotics

Acute Complications Hypoglycemia

- Defined as blood glucose < 70mg/dl
- Common causes:
  - A change in the content or timing of meals
  - An increase in physical activity
  - Too much medication (insulin, OHGA)
- Signs/Symptoms (interdiabetic perception varies)
  - <u>Mild</u>: irritability, confusion, tremors, diaphoresis, tachycardia, anxiety, hunger, headache (these symptoms are a result of epinephrine-the counterregulatory response to low blood glucose)
  - <u>Severe</u>: seizures, stupor, coma, death

Acute Complications Hypoglycemia

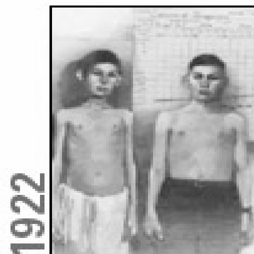
- <u>Treatment</u>
  - 1) 10-15gms rapidly absorbed CHO, repeat in 15 minutes if needed
    - milk 1/2 cup — orange juice 1/2 cup
    - apple juice 1/3 cup — grape juice 1/4 cup
    - sugar 2tsp/2 cubes — lifesavers 5-6 pieces
  - 2) Follow with complex CHO/protein repeat BG in 30 minutes (maintain BG of > 150mg/dl)
  - 3) If unconscious:
    - glucagon 0.5-1.0mg SQ, IM or IV (glucagon kit) <u>or</u>
    - glucose 25gms IV (dextrose 50%-50cc)

Insulin

- An anabolic hormone secreted from the B cells in the islets of Langerhans (pancreas)
- Primary function is to maintain a blood glucose level of 40-160mg/dl in conjunction with other counterregulatory hormones (glucagon, cortisol, epinephrine, GH)
- Transports glucose, amino acids and fatty acids into cells for their storage (glycogen, protein, triglycerides) and/or utilization

Insulin Milestones

- 1921: Discovery of Insulin (Banting & Best)
- 1922: First patient receives insulin
- 1923: First commercially available insulin
- 1940s: NPH available
- 1980: Purification
- 1982: Humulin® insulin introduced
- 1990s: DCCT & UKPDS
- 1996: Insulin analog



http://diabetes.lilly.com/

Insulin Sources

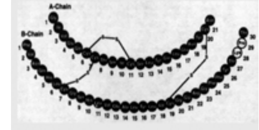
- Synthetic Human Insulin
  - Eli Lilly (Humulin)-recombinant DNA
  - Novo Nordisk (Novolin)-recombinant DNA
- Animal
  - *Beef*
  - *Pork*
- Immunogenicity: Beef>Pork>Human

Types of Insulin

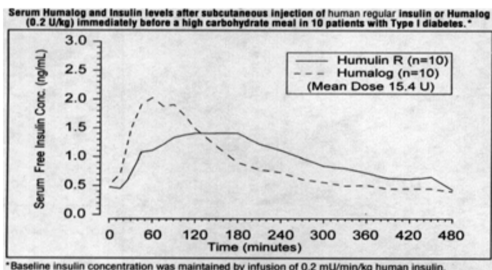
- Rapid-Acting (Lispro/Aspart/Glulisine)
- Short-Acting (Regular)
- Intermediate-Acting (NPH)
- Long-Acting (Ultralente/Glargine/Detemir)
- Premixed (NPH/Regular Combinations)
- Inhaled (Exubera™)

Insulin Rapid-Acting

- Lispro
  - Humalog™
- Onset: < 0.25 hrs
- Peak: 0.5-1.5 hrs
- Duration: 5 hrs
- "Meal Time" insulin
- More convenient for patient
- Less post-prandial hypoglycemia



Absorption of Lispro versus Regular Insulin



Available Products

- Insulin aspart – (Novolog – Novo Nordisk)
- Insulin lispro - (Humalog - Eli Lilly)
- Insulin glulisine – (Apidra – Aventis)

Drugs 1999; 57:759-65.

Lispro/Aspart/Glulisine Patient Counseling Issues

- This is a new insulin analog that should only be started under the supervision of a physician.
- It is currently only available by prescription.
- It's faster onset of action ***necessitates dosing 0-15 minutes before meals*** in contrast to 30-60 minutes with regular insulin.
- It's shorter duration of action may necessitate the need for a longer-acting insulin.

Insulin Short-Acting

- Regular
  - Humulin R, Novolin R, Velosulin R
  - Purified Pork, Semi-Lente Purified Pork (semi-lente no longer marketed)
- Onset: 0.5-1 hrs
- Peak: 2-4 hrs
- Duration: 5-7 hrs
- Injected 30-45 minutes before meals
- Only insulin that can be given I.V.

Insulin Intermediate-Acting

- NPH (isophane insulin suspension)
  - Humulin N, Novolin N, purified pork
- Lente (insulin zinc suspension)
  - Humulin L, Novolin L, purified pork
- Onset: 1-3 hrs
- Peak: 6-14 hrs
- Duration: > 24 hrs
- NPH is more commonly used due to mixing incompatibilities with Lente

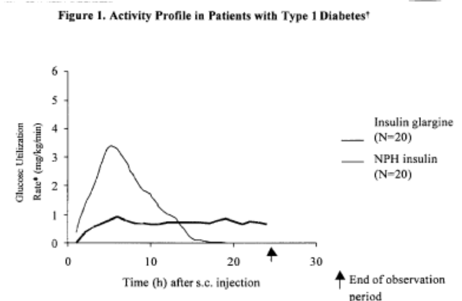
Insulin Long-Acting

- Ultralente (insulin zinc susp.-extended)
  - Humulin U
- Onset: 6 hrs
- Peak: 18-24 hrs
- Duration: > 36 hrs
- Used to provide "basal" levels of insulin between meals, not for suppressing acute glucose challenges (ie-meals).

Insulin Long-Acting

- Insulin Glargine (Lantus®)
  - Onset: 4 hrs
  - Peak: "peakless"
  - Duration: 24hrs
  - Administered SQ once daily
  - Possibly less hypoglycemia
- Insulin Detemir (Levemir®)
  - Binds to albumin
  - Duration: up to 24 hrs
  - Dosed 1-2 times daily
  - Less hypoglycemia compared to NPH
  - More consistent than insulin glargine??

Insulin Glargine - Lantus®



Insulin Premixed

- Humulin 70/30, Novolin 70/30, Humulin 50/50 (NPH/Reg)
- Humalog Mix 75/25 (lispro protamine/lispro)
- Advantages:
  - no mixing required
  - possibly less injections
- Disadvantages:
  - cannot adjust ratio in dosing

Insulin human inhalation powder (Exubera®)

- Indications
  - Treatment of DM in adults (type 1 and type 2 DM).
- MOA
  - The primary activity of insulin is regulation of glucose metabolism.
- Contraindications
  - Smokers
  - Poorly controlled lung disease

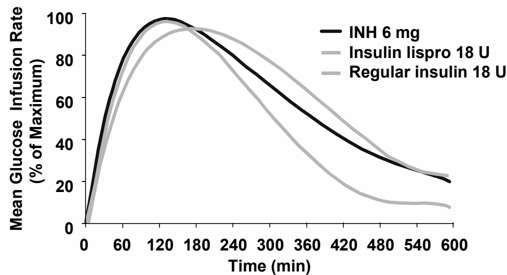
Insulin human inhalation powder (Exubera®)

- Adverse effects
  - Hypoglycemia
  - Respiratory effects
    - Cough, dyspnea, increased sputum production, dry mouth
    - Reversible decline in pulmonary function
  - Chest symptoms
- Monitoring
  - Assess pulmonary function prior to initiation

Insulin human inhalation powder (Exubera®)

- Pharmacokinetics
  - Onset similar to SQ administered rapid-acting insulin and duration of SQ adminstered regular insulin.
- Clinical Pearls
  - Inhale no longer than 10 minutes prior to meals
  - Dosing difference between 1mg and 3mg blisters
  - Close BG monitoring essential during respiratory illness
  - Each inhaler can be used for up to 12 months
- How supplied
  - Kit: Inhaler, replacement chamber, 1mg #180 blisters, 3mg #90 blisters, #2 release units

INH Absorbed More Rapidly than SC Regular; as Rapidly as SC Lispro - Study 017



Diabetologia 2000;43(Suppl 1):A46.

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Insulin human inhalation powder (Exubera®) Guidelines for AC Dose

Weight-KG	Weight-lbs	AC Dose	#-1mg blist.	#-3mg blist.
30-39.9	66-87	1mg	1	----
40-59.9	88-132	2mg	2	----
60-79.9	133-176	3mg	----	1
80-99.9	177-220	4mg	1	1
100-119.9	221-264	5mg	2	1
120-139.9	265-308	6mg	----	2

Insulin human inhalation powder (Exubera®) Guidelines-Converting from Human Regular

Dose (mg)	Regular Insulin Dose (units)	#-1mg Blisters	#-3mg Blisters
1mg	3	1	----
2mg	6	2	----
3mg	8	----	1
4mg	11	1	1
5mg	14	2	1
6mg	16	----	2

Insulin Pharmacokinetics

Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Appear.
Rapid-acting	< 0.25-0.5	0.5-2	5	Clear
Inhaled	0.25-0.5	0.5-1.5	3-7	Powder
Regular	0.5-1 hr	2-3	3-7	Clear
NPH	2-4	6-10	18	Cloudy
Lente	3-4	6-12	20	Cloudy
Ultralente	6	10-16	18-24	Cloudy
Glargine	4	-----	24	Clear
Detemir	2	8-12	16-24	Clear

Complications of Insulin Therapy

- Hypoglycemia
- Allergic Reactions
  - local skin reactions/systemic allergic reactions
- Insulin Resistance
- Lipoatrophy
  - immune response to insulin
  - appears 2 mos to several yrs after initiation
- Lipohypertrophy
  - lipogenic effects of insulin from repeated injections into same site
  - delays insulin absorption

Complications of Insulin Therapy

- "Honeymoon" period
  - a remission phase which can occur days to weeks after diagnosis which can last up to months
  - continue patients on low dose insulin
- Somogyi Effect
  - normoglycemia at hs→hypoglycemia at 3am→ hyperglycemia in the morning
- Dawn Phenomenon
  - a rise in BG concentrations of 30-40mg/dl between 4am and 8am possibly secondary to growth hormone
  - Follows an inconsistent pattern

Insulin Dosing Daily Requirements

Type 1-initial dose	0.5-0.6 U/kg
Type 1-"honeymoon" period	0.0-0.4 U/kg
Type 1-during illness/growth phase	0.5-1.0 U/kg
*Type 1-pregnant	0.7 U/kg
Type 2-insulin resistance	0.7-2.5 U/kg

This is an approximate initial schedule only
*requirements increase during 2nd and 3rd trimester

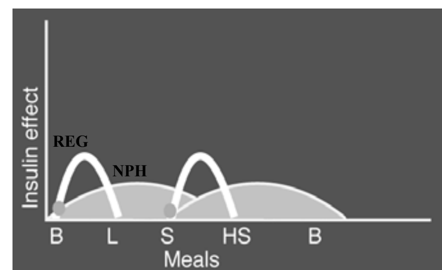
Multiple Daily Dosing Regimens

	30 min before breakfast	30 min before lunch	30 min before dinner	Bedtime
Method 1	NPH:Reg (2/3)		NPH:Reg (1/3)	
Method 2	NPH:Reg (2/3)		Reg (1/6)	NPH (1/6)
Method 3	Reg (1/4)	Reg (1/4)	Reg (1/4)	NPH (1/4)
Method 4	Reg (1/5) ULT (1/5)	Reg (1/5)	Reg (1/5) ULT (1/5)	
Method 5	RA (1/6)	RA (1/6)	RA (1/6)	Glar (3/6)

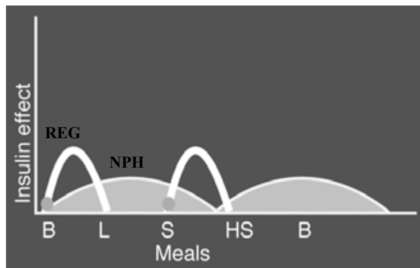
Multiple Daily Dosing Regimens (cont'd)

- Fractions in ( ) represent fraction of total daily dose administered at that time of day
- In some cases Lispro/Aspart can be substituted for Regular at the same dose but administered 0-15 minutes prior to meals
- Lente can be substituted for NPH
- Method 2: when the NPH is delayed until hs, the peak effect occurs around breakfast time rather than 2-3 am. Also some residual effect may help mid-morning hyperglycemia

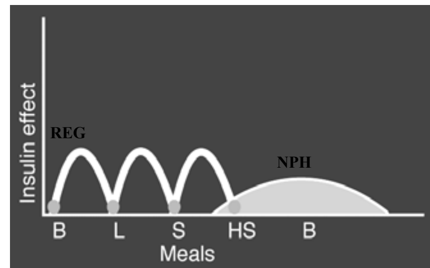
Method 1



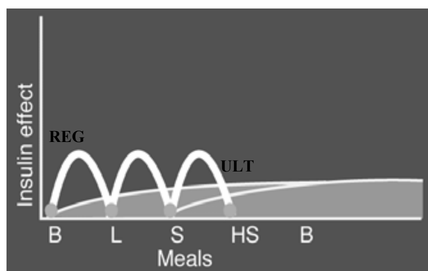
Method 2



Method 3



Method 4



Insulin Adjustments

Time	BG Value	Adjustment
FBS	High	↑ PM or HS N/L
FBS	Low	↓ PM or HS N/L
Before Lunch	High	↑ AM short-acting
Before Lunch	Low	↓ AM short-acting
Before Dinner	High	↑ AM N/L or lunchtime short-acting
Before Dinner	Low	↓ AM N/L or lunchtime short-acting
Before HS	High	↑ Dinner short-acting
Before HS	Low	↓ Dinner short-acting
During Night	Low	↓ PM N/L or move dinner N/L to HS

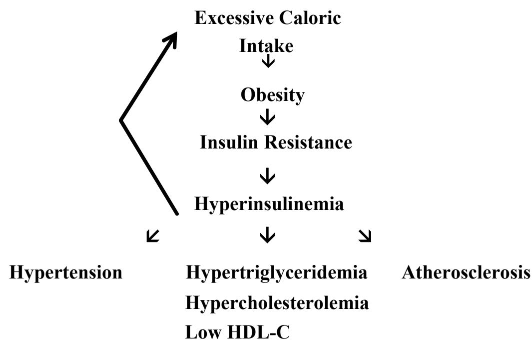
Treatment of Type 2 DM

- Oral Medications
  - Sulfonylureas
  - Biguanides
  - Alpha-glucosidase Inhibitors
  - Thiazolidinediones
  - Meglitinide/D-Phenylalanine Derivative
  - Fixed Combinations
- Parenterals
  - GLP-1
  - Amylin analog

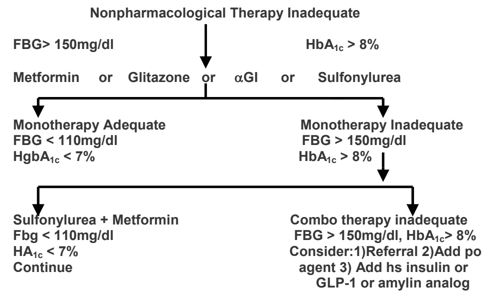
Oral Antidiabetic Agents Milestones

- 1955: Sulfonylureas introduced
- 1961: Berson & Yalow measure insulin levels-finding higher levels in Type 2 DM
- 1960s: Phenformin: introduced
- 1977: Phenformin withdrawn
- 1994: Metformin introduced
- 1995: Acarbose introduced
- 1997: Troglitazone introduced
- 1999: Rosiglitazone & Pioglitazone introduced
- 2000: Troglitazone withdrawn

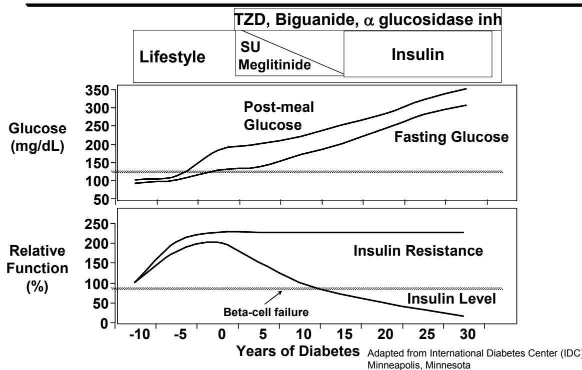
Syndrome of Insulin Resistance



Treatment Algorithm for Type 2 DM



Where are we now? Type 2 DM



Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota

Sulfonylureas Second Generation

Drug	Equiv.Dose(mg)	Min/Max Dose(mg)
Glipizide (Glucotrol & XL™)	5-10	2.5-40/day qd-bid
Glyburide (Diabeta &Micronase™)	5	1.25-20/day qd-bid
Micronized-Glyburide (Glynase Prestab™)	3	0.75-12/day qd-bid
Glimepiride (Amaryl™)	1-2	1-8/day qd

Sulfonylureas

- Indications: Type 2 DM, alone or in combination with insulin. Following diet & exercise
- MOA: Increases Beta-cell insulin secretion
  - Extrapancreatic effects (?)
    - reducing hepatic glucose production
    - increasing insulin receptor sensitivity
    - increasing the number of insulin receptors
- Adverse Reactions
  - Hypoglycemia
  - Gastrointestinal-N/V, cholestasis
  - Rash/pruritus

Sulfonylureas

- Inefficacy
  - Primary Failure-a patient who never responds satisfactorily to a sulfonylurea (incidence 5-10%)
  - Secondary Failure-occurs at a rate of 5-10% of pts per year who were initially well controlled on sulfonylureas
  - Patients that usually respond well to sulfonylureas are at least 40 yrs of age, have a FBG < 300mg/dl and have had type 2 DM < 5 years

Sulfonylureas

- Drug Interactions
  - Mostly associated with 1st generation
  - Increased hypoglycemic effect or Decreased hypoglycemic effect
- Doses of either glyburide or glipizide > 10mg/day generally result in little or no improvement in BG control
- Do not work well when BG is out of control
- Must be used with diet and exercise
- Use caution in renal impairment

Sulfonylureas Clinical Pearls

- Generally dosed 30 minutes before a meal
- Glyburide may provide better 24 hr glycemic control
- Glipizide may be more effective for post-prandial hyperglycemia
- Can use once a day dosing on glyburide if total daily dose is < 15mg
- Require intact Beta-cells to work

Sulfonylureas Clinical Pearls

- Give an agent enough time to work (1-2 mos) before adjusting or switching
- Maximize dose before switching to another agent (???)
- Generally, 1st & 2nd generation agents are equally effective
- 2nd generation agents are generally better tolerated than 1st generation agents
- Only 50% of patients continue to respond adequately to a sulfonylurea after 10 years

Biguanides Metformin (Glucophage™)

- Indications: Type 2 DM, alone or in combination with sulfonylurea. Following diet & exercise
- MOA
  - ↓ hepatic glucose production
  - ↓ intestinal absorption of glucose
  - improves insulin sensitivity, ↑ peripheral glucose uptake and utilization

Biguanides-Metformin

- Clinical Pearls
  - May induce weight loss
  - Positive effects on lipids: ↑ HDL, ↓ LDL & TG
  - Does not produce hypoglycemia (monotherapy)
  - Does not cause hyperinsulinemia
  - Works differently than sulfonylureas
  - Lowers BG concentrations approximately 20% more than with sulfonylurea alone

Biguanide-Metformin

- Precautions/Contraindications
  - Lactic acidosis
    - Incidence: 1 in 33,000 pts, 50% fatal
    - Avoid in pts with renal impairment, hepatic disease, CHF or hx of lactic acidosis
    - SCr must be < 1.5mg/dl-Ma, < 1.4mg/dl-Fe
    - Iodinated contrast materials-stop metformin, do not restart until 48 hrs after procedure complete
    - Signs-subtle onset, malaise, myalgias, abdominal distress, respiratory distress

Biguanides-Metformin

- Adverse effects
  - GI reactions-diarrhea, N/V, bloating, flatulence, anorexia (transient & dose related)
- Dosage & Administration
  - Metformin (Glucophage®)
    - Divide doses with meals and gradually ↑
    - 500mg qd or bid, ↑ weekly by 1 tablet, OR
    - 850mg q am, ↑ by 1 tab qowk to 2550mg/day
    - Max 2550mg, most effective dose 2000mg
  - Metformin XR (Glucophage XR ®)
    - 500mg once a day with pm meal to start, ↑ by 500mg/week to a max dose of 2000mg/day

Meglitinide/D-Phenylalanine

- Repaglinide (Prandin™)
  Nateglinide (Starlix®)
- Indications
  - Type 2 DM, as monotherapy or in combination with metformin. Following diet and exercise
- MOA
  - Stimulates insulin secretion from the Beta-cells of the pancreas using a unique binding profile

Meglitinide/D-Phenylalanine

- Clinical Pearls
  - Faster onset and shorter duration compared to sulfonylureas, dosed prior to meals to help manage prandial glucose loads
    - 15 minutes AC (repaglinide)
    - 1-30 minutes AC (nateglinide)
  - Possibly less hypoglycemia, due to shorter duration and less kidney excretion
  - Synergistic with metformin
  - Nateglinide has a shorter DOA vs. repaglinide

Meglitinide/D-Phenylalanine

- Adverse Effects
  - Comparable to sulfonylureas
  - Hypoglycemia-16% vs 20% with glyburide
  - Less weight gain (?)

Meglitinide/D-Phenylalanine

- Efficacy (Repaglinide)
  - A change in HbA_{1c} of (-)0.6% compared to baseline
  - Combo therapy with metformin resulted in a decrease in HbA_{1c} of 1.4% from baseline
- Efficacy (Nateglinide)
  - A change in HbA_{1c} of (-)0.5% compared to baseline
  - Combo therapy with metformin resulted in a decrease in HbA_{1c} of 1.5% from baseline

Meglitinide (Repaglinide)

- Dosage and Administration (Repaglinide)
  - For pts not previously treated with oral antidiabetic agents or HbA1c < 8%
    - 0.5mg before each meal
  - For pts previously treated with oral antidiabtic agents or HbA1c $\geq$ 8%
    - 1-2mg before each meal
  - The dose can be adjusted up to 4mg before each meal given up to 4 times/day (16mg)
  - Pts should be informed that if a meal is skipped the dose of repaglinide should be omitted

D-Phenylalanine (Nateglinide)

- Dosage and Administration (Nateglinide)
  - The recommended starting and maintenance dose is <u>120mg TID AC</u> (alone or in combo w/metformin)
  - For pts. near HbA1c goal-<u>60mg TID AC</u> (alone or in combo w/metformin)
  - Pts should be informed that if a meal is skipped the dose of nateglinide should be omitted

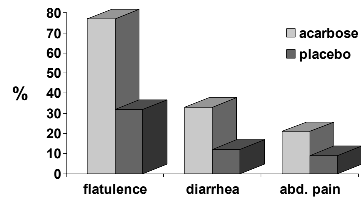
Alpha-Glucosidase Inhibitors

- Acarbose (Precose™) Miglitol (Glyset™)
- Indications: Type 2 DM, alone or in combination with a sulfonylurea. Following diet and exercise
- MOA
  - A complex oligosaccharide that delays the digestion of ingested carbohydrates
  - Competitive, reversible inhibition of pancreatic alpha-amylase and membrane bound intestinal alpha-glucoside hydrolase enzymes
  - Results in delayed sugar absorption and a lowering of post-prandial hyperglycemia

Alpha-Glucosidase Inhibitors

- Clinical Pearls
  - Effects are additive with sulfonylureas
  - May diminish the weight-increasing effects of sulfonylureas
  - Does not cause hypoglycemia when given as monotherapy
- Adverse Effects
  - GI: F-L-A-T-U-L-E-N-C-E, diarrhea, abdominal pain
    - Resolves with time

Acarbose Adverse Effects



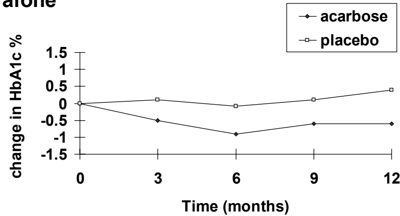
Alpha-Glucosidase Inhibitors

- Precautions/Contraindications:
  - Intestinal obstruction
  - Hypoglycemia
    - should not cause hypoglycemia when given alone
    - oral glucose (dextrose), should be used instead of sucrose to treat hypoglycemia. Sucrose/fructose are inhibited by acarbose/miglitol

Alpha-Glucosidase Inhibitors

- Dosage and Administration
  - Acarbose (Precose™)
    - TID with each main meal (w/ first bite of food)
    - Initially: 25mg po tid
    - Maintenance: 50 -100mg TID
    - If < 60 kg maximum is 50mg TID
  - Miglitol (Glyset ™)
    - Month 1: 25mg q dinner x 2 weeks, then 25mg q breakfast and dinner x 2 weeks
    - Month 2: 25mg tid w/meals x 1 month
    - Month 3: 50mg tid
    - Max dose: 100mg tid w/meals

Acarbose vs. Placebo



Thiazolidinediones

- Rosiglitazone (Avandia™)
  - Indications: Monotherapy or Combination with Metformin for Type 2 DM following diet and exercise
- Pioglitazone (Actos™)
  - Indications: Monotherapy or Combination with Metformin, Sulfonlyureas or Insulin for Type 2 DM following diet and exercise

Thiazolidinediones

- MOA (Agonist of PPARγ)
  - Lowers BG by ↑ target cell response to insulin
  - ↓ hepatic glucose output and ↑ insulin-dependent glucose disposal in skeletal muscle
- Monitoring of LFTs
  - Baseline and periodically thereafter

Thiazolidinediones

- Precautions/Contraindications
  - Monitor LFT's
  - Ovulation-resumption of ovulation occurred in premenopausal anovulatory women
  - Hypoglycemia-generally only in combo therapy
  - Precipitation of CHF

Thiazolidinediones

- Adverse Effects
  - May cause moderate weight gain/edema
  - Increase cholesterol levels
    - ↑ LDL & HDL, ↓ Triglycerides
- Drug-Drug Interactions
  - Oral contraceptives-↓ OC levels by 30%
  - Sulfonylureas/insulin-↑ risk of hypoglycemia

Thiazolidinediones

- Efficacy
  - ↓ in HbA_{1c} 0.84-1.5%
  - ↓ in insulin requirement
- Dosage and Administration
  - Pioglitazone:15-45mg/day
  - Rosiglitazone: 4-8mg/day, once daily or as BID dosing

Thiazolidinediones

- **Clinical Pearls**
  - **Effective at increasing insulin sensitivity in most Type 2 diabetics and non-diabetic patients with impaired glucose tolerance**
  - **Probably most effective in obese patients in improving insulin resistance**
  - **Well tolerated, less hypoglycemia and GI effects than other oral agents**
  - **Initial response 2-4wks, peak response 6-12 wks**

GLP-1

- Exenatide (Byetta™)
- Indications
  - **Type 2 DM not controlled by:**
    - **Metformin**
    - **Sulfonylurea**
    - **Metformin + Sulfonylurea**

- MOA
  - **Enhances glucose-dependent insulin secretion by the beta-cells, suppresses inappropriately elevated glucagon secretion and slows gastric emptying**
  - **Other effects: weight loss, decreased food intake**

GLP-1

- Adverse effects
  - **Hypoglycemia-when given with sulfonylurea (15-35%)**
  - **Nausea 44%, Vomiting 13%, Diarrhea 13%**
  - **Jittery 9%**
- Precautions
  - **ESRD, severe renal disease, severe GI disease**
- Efficacy
  - **0.6-0.9% ↓ in HbA_{1c}**

GLP-1

- Dose
  - **5mcg subcutaneously BID (AC) x 4 weeks, may increase to 10mcg BID if needed**
- Storage
  - **Refrigerate, protect from light and do not freeze**
  - **Discard product 30 days after first use**
- Available
  - **5mcg dose, 1.2ml prefilled pen (60 doses)**
  - **10mcg dose, 2.4ml prefilled pen (60 doses)**
  - **$ ≈ $180-$210 AWP**

Amylin Analog

- Pramlintide (Symlin®)
- Indications
  - **Type 1 and Type 2 DM**
    - **Not controlled by multidose insulin**
- MOA
  - **Amylin analog**
  - **Reduces glucagon secretion**
  - **Slows gastric emptying**
  - **Other effects: weight loss, decreased food intake**

Amylin Analog

- Adverse effects
  - **Nausea ≈ 30-40%**
  - **Severe hypoglycemia ≈ 5%**
- Contraindications
  - **Diagnosis of gastroparesis**
  - **Hypoglycemia unawareness**
  - **Not studied in pediatrics**
- Efficacy
  - **HbA1c reduction: 0.4-0.6%**
  - **Weight loss: 1-2 kg**
  - **% reduction in short/rapid acting insulin dose: 3-4%**

Amylin Analog

- Dosing for Type 2 DM
  - **Step1**
    - **Reduce pre-meal insulin dose by 50%**
    - **Start 60mcg subcutaneously AC**
    - **Monitor BG frequently (AC, PC, HS)**
  - **Step 2**
    - **Increase dose to 120mcg subcutaneously AC when nausea free for 3-7 days**
    - **If nausea persists reduce back to 60mcg**
  - **Step 3**
    - **Adjust insulin accordingly**
  - **Step 4**
    - **Ongoing patient assistance**

Amylin Analog

- Dosing for Type 1 DM
  - **Step1**
    - **Reduce pre-meal insulin dose by 50%**
    - **Start 15mcg subcutaneously AC**
    - **Monitor BG frequently (AC, PC, HS)**
  - **Step 2**
    - **Increase in 15mcg increments to a maintenance dose of 30-60mcg as tolerated**
    - **Increase to next increment when nausea free x 3 days**
    - **If nausea persists at 45-60mcg reduce to 30mcg**
    - **Consider d/c if 30mcg not tolerated**
  - **Step 3**
    - **Adjust insulin accordingly**
  - **Step 4**
    - **Ongoing patient assistance**

Amylin Analog

- Storage
  - **Refrigerate prior to use**
  - **Opened vials can be stored at room temp x 28 days**
- Available
  - **5ml vials (0.6mg/ml)**
  - **See PI for conversion chart (mcg to ml)**
    - **15mcg = 0.025ml, 30mcg = 0.05ml……**
- Other
  - **Do not mix with insulin**
  - **Inject into abdomen or arm**
  - **≈ $100 AWP (≈ $90-$360/month)**

Fixed Combination – Oral

- **Glyburide / Metformin (Glucovance™)**
  - **1.25mg/250mg**
  - **2.5 mg/500 mg**
  - **5.0 mg/500 mg**
- **Indications:**
  - **Initial therapy**
  - **Second line after SU or biguanide monotherapy failure**

Diabetes 2000; 49 (Suppl 1): A415; A416; A432; A1493; A1498

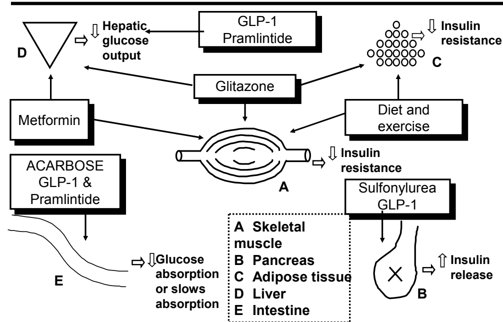
Fixed Combination – Oral

- **Metformin/Rosiglitazone (Avandamet™)**
  - **1mg/500mg**
  - **2mg/500mg**
  - **4mg/500mg**
- **Indications**
  - **Already taking the combo**
  - **Inadequately controlled on metformin**
- **Maximum Dose**
  - **8mg/2000mg**

Fixed Combination – Oral

- **Glipizide and Metformin (Metaglip™)**
  - **2.5mg/250mg**
  - **5mg/250mg**
  - **5mg/500mg**
- **Indications**
  - **Adjunct to diet and exercise**
  - **Not adequately controlled on metformin or glipizide**
- **Max dose: 20mg/2000mg**

Current Treatment Strategies for Insulin Resistance



Opara JU, et al. *South Med J.* 1997;90:1166.

Case Study #1

- E.P. is an obese 46 yo hispanic male presenting to the clinic with complaints of fatigue and nocturia. He reports that he has not felt "decent" for at least 4 months. The patient also complains that he seems to have had more "colds" than usual this past winter. E.P. does not exercise and admits to a poor diet.
- PMH: HTN x 6 years, Rheumatoid Arthritis x 4 years
- FH: Brother-diabetes, Father-diabetes, Sister-HTN
- SH: (+) tobacco 1PPD, (+) etoh 1 beer/day
- Meds: Metoprolol 50mg BID, Prednisone 5mg daily, HCTZ 12.5mg daily, Apap 500mg Prn
- Vitals: Height 5'10", Weight 100kg, BP 156/96, Pulse 72
- Allergies: NKMA

Case Study #1

- Labs: BG (random) 225mg/dl (70-110), HbA1c 11% (4-7), LFT's-WNL, SCr 1.1mg/dl (0.5-1.2), U/A (+) glucose, (-) ketones
- A fasting BG is drawn in the clinic the following week with a value of 157mg/dl and the patient is given the diagnosis of Type 2 DM. What features in the above history are consistent with this? Are there any other possible causes?
- Over the next 3 months the patient makes dramatic lifestyle changes by following a formal diet plan and exercising on a daily basis, his HbA1c however is still 10%. The physician wants to begin an oral diabetic agent but cannot decide between metformin and a sulfonylurea and asks for your suggestion. Which would you choose and why?

Case Study #2

- E.P. is a 46yo hispanic male following up in the clinic for his recently diagnosed type 2 DM. The patient is very motivated to achieve "tight" control because his diabetic brother is currently experiencing severe neuropathy. The patient is following an appropriate diet and walking 1 hour/day. He has been on Metformin 500mg #2 po BID x 6 months and has tolerated it well except for some initial GI complaints which have since resolved. The patient's current HbA1c is 8.5%.
- Meds:
  - Metformin 500mg #2 po BID, Metoprolol 50mg BID, HCTZ 12.5mg daily, Motrin 800mg TID Prn, Apap 500mg Prn
- Vitals: Height 5'10", Weight 94kg, BP 145/92, Pulse 66
- SH: (+) tobacco 1PPD, (+) etoh 1 beer/day

Case Study #2

- What would be an optimal HbA_{1c} for this patient?
- List two agents that would be appropriate to add to this patient's regimen to improve his HbA_{1c}. Discuss the pros and cons of the agents.
- Are the patient's BP medications appropriate? Explain. Is there a better choice? What is the patient's target BP goal?