Diabetes Mellitus: Pharmacology and Disease Management

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Objectives

1. Compare pharmacologic interventions for patients with diabetes.

2. Optimize management of diabetes to decrease potential microvascular and macrovascular complications.

Therapies

- Constantly evolving treatments & evidence
- Important to know the type and physiology of diabetes
- Type 1:
  - Insulin (many types and preparations)
  - Some new options (pramlintide)
- Type 2:
  - Oral agents and/or insulin/and or new options

Selecting an Oral Agent

Considerations:

- Efficacy for glycemic reduction
- Mechanism of action
- Side effects/contraindications
- Associated metabolic changes
- Patient adherence
- Cost

T2DM Treatments and Decrease in A1C

Drug Class	HbA1c % Decrease
Sulfonylureas (Glyburide, Glipizde, Glimepiride)	1.0 to 2.0
Meglitinides (Repaglinide, Nateglinide)	0.5 to .5
Biguanides (Metformin)	1.0 to 2.0
Glitazones (Rosiglitazone, Pioglitazone)	0.5 to 1.4
Alpha-Glucosidase Inhib. (Acarbose, Miglitol)	0.5 to 0.8
Amylin Analogue (Pramlintide)	0.5 to 1.0
Incretin Mimetic (Exenatide)	0.5 to 1.0
DPP-4 Inhib (Sitagliptin)	0.5 to 0.8

Pathophysiologies and Pharmacotherapy Mechanisms of Action

	Insulin deficiency	Insulin Resistance	Excess hepatic glucose output	Intestinal glucose absorption
Sulfonylureas	✓			
Meglitinides	✓			
Metformin		✓	✓	✓
Glitazones		✓	✓	
Alpha-Glucosidase Inhib.				✓
DPP-4 Inhib.	✓		✓	

ADA Algorithm for Management of Type 2 Diabetes

LESS well-validated therapies after lifestyle and Metformin

- Step 2:
  - Add Pioglitazone (if no hypoglycemia, edema, HF, bone loss)
    OR
  - Add GLP-1 agonist (if no hypoglcemia, weight loss, nausea/vomiting)
- Step 3:
  - Combination of preferred Sulfonylurea and Pioglitazone (no GLP-1 agonist) OR
  - Add basal insulin (no sulfonylurea, pioglitazone, or GLP-1)
- Final: Add Intensive Insulin

Diabetes Care, Vol. 32, 2009, 193–203

Insulin Secretagogues

- Sulfonylureas: Long acting agents
  - Second generation: glipizide, glyburide, glimepiride
  - Cheapest oral medication
- Meglitinides: Short acting (<1hr half life)
  - Repaglinide (Prandin), Nateglinide (Starlix)
  - Expensive
- Combinations
  - Glyburide/Metformin (Glucovance), Glipizide/Metfomin (Metaglip), Rosiglitazone/Glimepiride (Avandaryl), Pioglitazone/Glimeperide (Duetact)

Sulfonylureas

- Little benefit beyond half of max dose
- Risks: Hypoglycemia, weight gain
- Renal Insufficiency/Failure:
  - Avoid Glyburide (active metabolites, renally cleared)
  - Glipizide (Glucotrol), inactive metabolites, and glimepiride (bilary/fecal excretion) preferred

Sulfonylureas

- Many drug interactions:
  - ↑ action (NSAIDs, warfarin, salicylates, allopurinol, alcohol, B-blockers)
  - ↓ action (steroids, diuretics, L-thyroxine, estrogen/progestins)
- Decreases Microvascular enpoints, only trends toward decreasing macrovascular (UKPDS).

Biguanide: Metformin

- Decreases hepatic glucose production (main)
- Increased muscle glucose utilization (less prominent)
- Combines well with SU, acarbose, glitazones, DPP4 inhib or insulin
- Preffered Initial Treatment:
  - Less hypoglycemia, wt loss, enhances lipids, improves insulin resistence
  - Improves macrovascular enpoints (UKPDS)

Metformin : Contraindications

- Renal insufficiency
  - Serum CR >1.5 males, >1.4 females
- Hepatic insufficiency
- CHF
- Dehydration
- ETOH abuse
- Hx of metabolic acidosis
- Type I diabetes
- Category B in Pregnancy

Metformin: Side Effects and Caveats

- Nausea, diarrhea: may be self limited
- Lactic acidosis; Identify risk factors
- Hold with IV contrast (48 hrs before)
- Uncommon to see benefit past 2000mg per day (max of 2550 mg)

Metformin: New Preparations

- Glucovance = metformin + glyburide
- Metaglip = metformin + glipizide
- Avandamet = metformin + rosiglitazone
- Actosplus met = metformin + pioglitazone
- Janumet = metformin + januvia

- The same precautions apply

Thiazolidendiones

- Increases peripheral insulin sensitivity
  - Activates PPAR (peroxisome proliferator activated receptor gamma)
- Combination therapy with insulin, SU, metformin (mentioned previously)

Glitazones: General considerations

- Do not use if baseline LFTs >3x normal
- Can precipitate clinical heart failure so use cautiously
- Contraindicated with NYHA HF Class III-IV
- CVD? Black box warning

Glitazones: A Benefit or Harm?

- Data is clear to support A1C reduction (disease surrogate)
- No clear difference clinically in other oral hypogylcemic therapies
- No clear evidence to support improved patient oriented outcomes (mortality, MI, CVA)
- Some evidence supports increased CV risk of events, edema and HF episodes/ hospitalization

Richter,B, et al. *Cochrane Database Syst Rev.* 2007; (3).
Richter,B, et al. *Cochrane Database Syst Rev.* 2006; (4).
Nissen, SE, et al. *NEJM.* 2007;356:2457-71.

Remember Glucagon?

- Effects of glucagon in glucose metabolism and utilization
- Suppressing something instead of increasing something
- Homoestasis = sum of the parts
  - Alpha α + Beta β = Glucose Control
  - Glucagon and Insulin
- Newer products focus on this physiology:
  - Amylin analogue, Incretin Mimetic and DPP-4 Inhibitors

Pramlintide (Symlin): Synthetic Amylin

- Amylin:
  - Produced with insulin (beta cells)
  - Works with insulin and glucagon to maintain normal blood glucose
  - As beta cell function declines, diabetics become Insulin and Amylin deficient
- Effects:
  - suppress glucagon excretion
  - control postprandial hyperglycemia
  - delay gastric emptying, promote satiety
- Approved:
  - Type 1 diabetes, not achieving goal A1C
  - Type 2 diabetes, using insulin and not at goal.

Pramlintide

- SC Injection before meals
  - Lowers post prandial glucose
  - Less fluctuation during the day
  - Less mealtime insulin necessary
  - Cannot be combined with insulin.
- Improves A1C control compared to insulin alone.
- Reduction in body weight compared to insulin alone.
- Expensive

Pramlintide: Side Effects

- Mainly nausea (Dose dependent)
- Hypoglycemia with insulin
- Others: fatigue, abd pain

- No Cardiac, Hepatic or Renal toxicity
- No lipid abnormalities

Medical School Revisited?

- Incretins: intestinal hormones released during eating
  - GIP: glucose dependent insulino-tropic peptide
  - GLP1: glucagon-like peptide
- ~ 60% of post-meal insulin secretion due to incretins (impaired in T2DM)
- Dipeptidyl peptidase-4 enzyme (DPP-4): inactivates GLP1 and GIP

GLP-1 and Glucose Homeostasis

- Enhances **glucose dependent** insulin secretion, AND
- Suppresses glucagon secretion
- Promotes satiety, leading to reduction of food intake
- Regulates the rate of gastric emptying, limiting postprandial glucose excursions

Incretin Mimetic: Exenatide (Byetta)

- Amino acid sequence partially overlaps that of the human incretin hormone GLP-1
- T2DM, not achieved target A1C levels with metformin, sulfonylurea, or combination.
- Approved in combination with Metformin and Sulfonylureas
- No hypoglycemia unless taken with a sulfonylurea.
  - Consider decreasing sulfonylurea dose

Exenatide: Caveats

- Not an insulin substitute in insulin-requiring patients
- Not for use Type 1 DM or with DKA
- Not recommended in patients with end-stage renal disease or renal impairment (GFR <30), or severe gastrointestinal disease
- Pancreatitis??
- Category C in Pregnancy

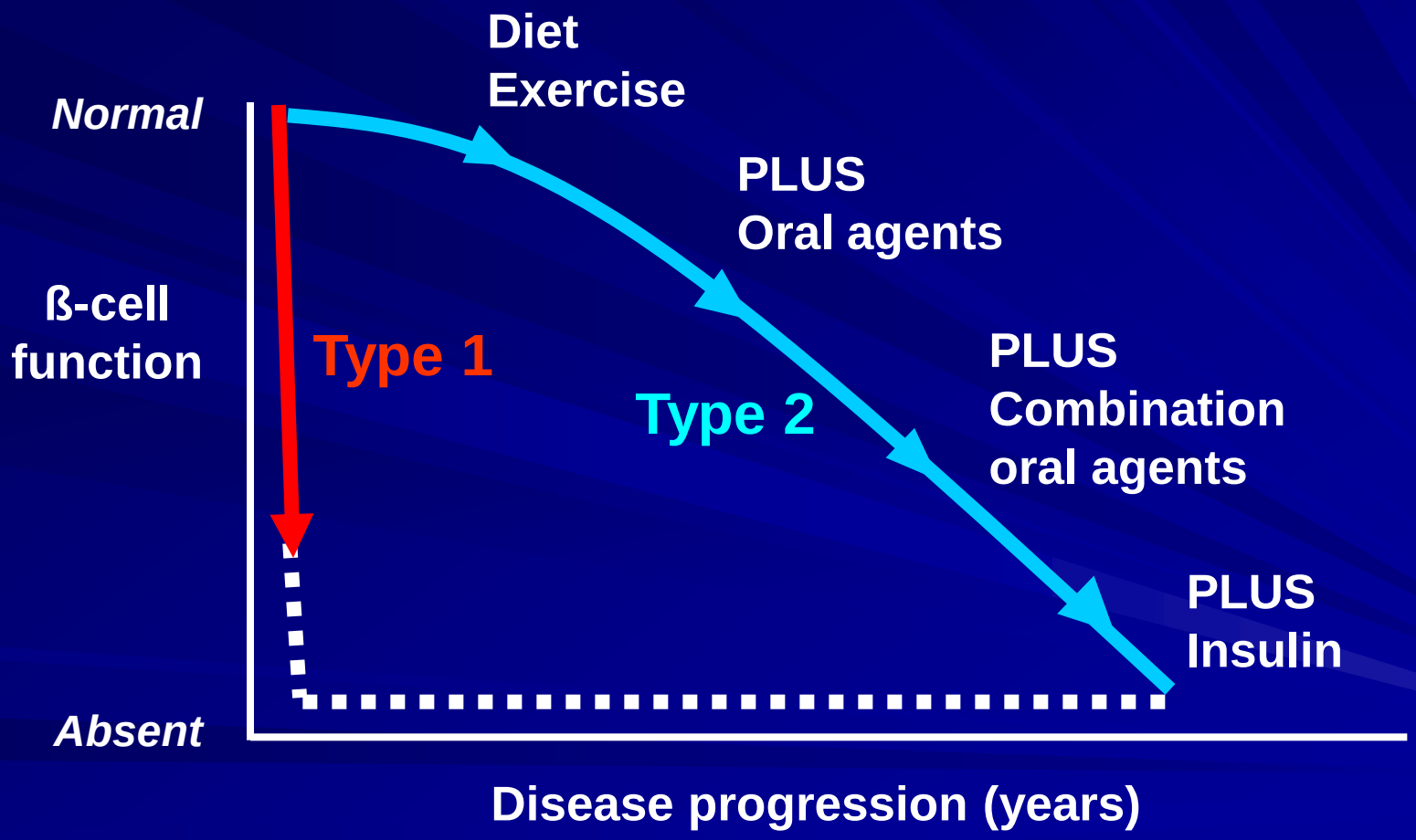
DPP4 Inhibitors

- Sitagliptin (Januvia, 2006) and Saxagliptin (Onglyza, 2009)
- DPP4 inhibitors
  - Improves A1C, fasting and post-prandial glycemia
- Oral Monotherapy, with metformin or a glitazone
- Not for Type 1 DM
- Recommended doses:
  - Sitagliptin 100 mg PO QD
  - Saxagliptin 5 mg PO QD

DPP-4 Inhibitors
Side Effects and Cautions

- Adverse reactions was similar to placebo, including hypoglycemia, some concern of slight increase in upper respiratory infections
- Renal Insufficiency
  - No renal toxic effects but is efficacious at lower doses in renal insufficiency and ESRD (even hemodialysis)
  - Sitagliptin:
    - 50mg: Moderate RI, CrCl <50 but >30 mL/min (Cr >1.7 in men, >1.5 in women)
    - 25mg: Severe RI, Cr Cl <30 mL/min (Cr >3.0 in men, >2.5 in women)
  - Saxagliptin:
    - 2.5 mg daily, Moderate or Severe RI, CrCl ≤50 mL/min

Insulin: Sometimes a Necessary Therapy



Insulin Therapy

- Useful for both type 1 and type 2
- Basal bolus
- Mimic normal physiology
- Know the timing
- Basal or longer acting: NPH, glargine
- Bolus: regular, lispro, aspart

ADA Algorithm for Management of Type 2 Diabetes

Well-Validated Core Therapies

- Step 1: at Diagnosis
  - Lifestyle Modification and Metformin
- Step 2: Add Basal Insulin OR
  - Add preferred Sulfonylurea
    - Not glyburide or chlorpropamide
    - If fails then stop sulfonylurea and add basal insulin
- Step 3: Add Intensive Insulin

Diabetes Care, Vol. 32, 2009, 193–203

Oral Agents + Insulin Type 2 Diabetes:

- Improves glycemic control
- Lower doses of exogenous insulin
- Addresses multiple causes of hyperglycemia

Insulin Initiation and Titration

1. Start q hs ***NPH or Glargine (10 U or 0.2 U/kg)*** → BS <70, ↓ 4U or 10%, whichever is greater

2. ✓Daily BS, ***↑ 2U q3d*** until fasting controlled, or ***↑ 4U q3d*** if >180

3. A1C >7, Fasting BS 70-130, then need 2nd Injection of Insulin

✓ BS	↑ pre-Lunch	↑ pre-Dinner	↑ pre-Bed
Add 2nd Injection	***Rapid Insulin*** at Breakfast	***NPH*** at Breakfast **or** ***Rapid Insulin*** at Lunch	***Rapid Insulin*** at Dinner

4. A1C >7, recheck pre-meal BS, may need 3rd Injection of Insulin as above

5. A1C >7, check 2hr postprandials and adjust preprandial ***Rapid-Insulin***

Diabetes Care, Vol. 32, 2009, 193–203

Insulins: Basal Therapy Fasting Control

Insulins	Onset	Peak	Duration
Long-Acting Analogues:			
Glargine (Lantus)	2-3 hrs	None	24+ hrs
Detemir (Levemir)	1 hr	None	up to 24 hrs
Intermediate Acting:			
NPH	1-3 hrs	4-10 hrs	10-18 hrs

Insulins: Bolus Therapy Prandial Control

Insulins	Onset	Peak	Duration
Rapid Acting Analogues: Lispro (Humalog) Aspart (Novolog) Glulisine (Apidra)	10-15 mins	1-2 hrs	3-5 hrs
Short Acting: Regular	0.5-1 hr	2-4 hrs	4-8 hrs

Insulins: Premixed Prandial Control

Insulins	Onset	Peak	Duration
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	10-15 mins	1-3 hrs	10-16 hrs
70/30 = 70% NPH / 30% regular 50/50 = 50% NPH / 50% regular	0.5-1 hr	2-10 hrs	10-18 hrs

Summary

- Diabetes management is individualized and involves the patient and a provider-directed team
- Establishing tight glycemic control is the key to management
- Lifestyle changes to prevent onset of diabetes and CVD are the first step
- Type 2 diabetes is progressive; management will likely ultimately require insulin
- Providers should employ an aggressive, treat-to-target strategy