Type 2 Diabetes: Treating an Epidemic

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Objectives

• Discuss the health and economic burden of diabetes
• Discuss necessary lifestyle modifications
• Describe the advantages and disadvantages of drugs used for diabetes
• Determine the appropriate drug therapy to optimize glycemic control in individual patients

Diabetes Trends* Among Adults in the U.S., (Includes Gestational Diabetes)

BRFSS 1995-96
Source: Mokdad et al., Diabetes Care 2000;23:1278-83.

Diabetes Trends* Among Adults in the U.S., (Includes Gestational Diabetes)

BRFSS 1997-98
Source: Mokdad et al., Diabetes Care 2001;24:412.

Diabetes Trends* Among Adults in the U.S., (Includes Gestational Diabetes)

BRFSS 1999
Source: Mokdad et al., Diabetes Care 2001;24:412.

Diabetes Trends* Among Adults in the U.S., (Includes Gestational Diabetes)

BRFSS 2000
Diabetes Trends* Among Adults in the U.S.,
(Incudes Gestational Diabetes)
BRFSS 2001

Source: Mokdad et al., J Am Med Assoc 2001;286:10

US Prevalence Data

• Total: 20.8 million people have diabetes
  Diagnosed: 14.6 million people
  Undiagnosed: 6.2 million
• 1.5 million new cases diagnosed in people ≥20yrs in 2005
• Pre-Diabetes: 41 million people


Healthcare Cost

Estimated US cost in 2002
• Total: $132 billion
  Direct medical costs: $92 billion
  Indirect costs: $40 billion


Complications

• Heart disease and stroke account for 65% of deaths
  Risk for stroke is 2 to 4 times higher
• 73% have BP >130/80mmHg or use medications
• Leading cause of new cases of blindness among adults aged 20-74yrs


Complications

• Leading cause of kidney failure, accounting for 44% new cases in 2002
• 60-70% have mild-severe forms of nervous system damage
• > 60% of non-traumatic lower-limb amputations occur in diabetes
• 1/3 have severe periodontal disease


Prevention with Goals

• Blood Pressure: < 130/80mmHg
• Lipids: LDL < 100mg/dL or < 70mg/dL (CAD)
• Preventative Care: Eyes, Kidneys, & Feet

Achieving Glycemic Control

- Every 1% reduction in A1c reduces microvascular complications by 40%.

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>&lt; 7.0%</td>
<td>&lt; 6.5%</td>
</tr>
<tr>
<td>Fasting BG</td>
<td>90-130 mg/dL</td>
<td>&lt; 110 mg/dL</td>
</tr>
<tr>
<td>2-hr PPG</td>
<td>&lt; 180 mg/dL</td>
<td>&lt; 140 mg/dL</td>
</tr>
</tbody>
</table>

Power of A1c Reduction:
The United Kingdom Prospective Diabetes Study

- 5,102 newly diagnosed w/ type 2 diabetes
- Conventional diet therapy vs. intensive medication (chlorpropamide, glyburide, metformin and insulin)
- Endpoints: diabetes related events, diabetes related death, all cause mortality
- Mean follow up: 10 years

Macrovascular Risk Reduction

- PROactive
  - Actos reduces the composite of all cause mortality, non-fatal MI, and stroke by 16% (NNT: 48 patients for 3 years)
  - Subgroup analysis: Actos significantly reduced the risk of second MI and ACS- 22 MI and 23 ACS over 3 years
- UKPDS 34- metformin alone
  - ↓ MI by 39% (p=0.01)
  - All macrovascular endpoints (p=0.02)

Diabetes Prevention Trial: Nutrition and Exercise

- Population: 3234 people with IFG and/or IGT; mean age 51 years; mean BMI 34
- Randomization: Placebo, Metformin 850 mg BID, Lifestyle modification program
- Mean follow up: 2.8 years
- Outcome: Diabetes Diagnosis

<table>
<thead>
<tr>
<th>Year</th>
<th>DM Incidence Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Placebo</td>
</tr>
<tr>
<td>1.5</td>
<td>Metformin</td>
</tr>
<tr>
<td>2.5</td>
<td>Lifestyle</td>
</tr>
<tr>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td></td>
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</tbody>
</table>

Diabetes Prevention Trial: Nutrition and Exercise

- DM Incidence Reduction: Lifestyle Modification: 58% & Metformin: 31%
- For a three year period the NNT with lifestyle modification is 6.9 and 13.9 for metformin.
Treatment Targets

- Insulin Secretion
- Hepatic Glucose Output
- Insulin Resistance

Treatment Options

<table>
<thead>
<tr>
<th>Primary Action</th>
<th>Insulin Secretion</th>
<th>Hepatic Glucose Output</th>
<th>Insulin Resistance</th>
<th>Gastric Emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretagogues</td>
<td>Glitazones</td>
<td>Incretin Mimetic</td>
<td>Amylin Analog</td>
<td>- Glycosidase inhibitors</td>
</tr>
<tr>
<td>Secondary Action</td>
<td>Glitazones</td>
<td>Incretin Mimetic</td>
<td>Amylin Analog</td>
<td>Biguanide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glitazones</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incretin Mimetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amylin Analog</td>
</tr>
</tbody>
</table>

“P.R.I.M.E Approach”

Primary Problem
Reasonable Therapy
Issues with Therapy
Monitoring Parameters
Expectations

Case #1

56 y/o AA female
Height: 5’4” Weight: 159lbs
HPI: Type 2 DM, HTN, Hyperlipidemia
Medications: Diovan-HCT®, verapamil, Zocor®, Glucovance® 2.5/500 ACB, 1.25/250 ACS, ASA
Labs: A1c 5.6, TC 154, LDL 72, HDL 72, TG 50
SCR and LFT’s WNL

Medications: Glucovance® 2.5/500 ACB, 1.25/250 ACS
**Sulfonylureas**  
Amaryl®, Glucotrol®, and Diaβeta®

**Non-SU Secretagogues**  
Starlix® and Prandin®

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**Sulfonylureas (SU):**  
**Things to Know**

- Agents equally effective
- Efficacy: ↓ A1c by 1-2%
- Maximum therapeutic effect in 5-10 days
- Ceiling Dose Effect  
  75% efficacy with 50% maximum dose
- Hypoglycemia  
  UKPDS 33: major events 0.6% vs 0.1% with diet
- Weight Gain  
  Typically reported as 2-5kg (UKPDS 33, ↑ 1.7 Kg)
- Secondary Failure

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**Sulfonylureas:**  
**Noteworthy Differences**

- Diaβeta®-glyburide  
  - May require twice daily dosing  
  - Slightly increased incidence of hypoglycemia
- Glucotrol®-glipizide  
  - Absorption ↓ by food (dose 30 min AC)
- Amaryl®-glimepiride  
  - Slightly less hypoglycemic episodes  
  - Longest duration of action

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**Non-SU Secretagogues:**  
**Things to Know**

- Reduced DOA as compared to SU
- Efficacy: ↓ A1c by 1-2%
- Administer up to 30 minutes prior to meals
- ↓ Frequency of hypoglycemia and weight gain compared to SU
- ↑ Dose adjustment intervals in pts with renal or hepatic impairment
- No concern with sulfa allergy

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**Non-SU Secretagogues:**  
**Noteworthy Differences**

- Prandin®-repaglinide  
  - Multiple drug interactions
- Starlix®-nateglinide  
  - Comparatively less reduction in A1c  
  - Relatively glucose dependant
Case #2

40 y/o WF
Height: 5’5”  Weight: 237lbs
HPI: Type 2 DM
Medication: Metformin 500mg BID
Labs: A1c 7.1, TC 192, LDL 99, HDL 49, TG 220
SCR and LFT’s WNL

Biguanide
Glucophage®-metformin

Metformin: Things to Know

- Mechanism of Action
  - Decreased hepatic glucose production
  - Reduced insulin resistance
  - Reduced gastric emptying time
- Increased A1c ↓ at higher BG levels
- 85% maximal effect seen with 1500 mg/day
- Onset of Action: ↓ FBS within 3-5 days
- Drug Interaction: Tagament® and IVP dye

Metformin: Additional Benefits

- Effect on lipids: ↓ LDL and TG, ↑ HDL
- Macrovascular benefits
- ↓ Pro-thrombotic state
- Weight neutral/loss
- No hypoglycemia when used alone
Case #3

67 y/o WM  
Height: 6'1"  Weight: 190lbs  
HPI: Type 2 DM, HTN, Hyperlipidemia, CAD  
Medications: Glucotrol XL® 5 mg po ACB, Atenolol, Lipitor®, Lopid®, Fish Oil, ASA  
Labs: A1c 7.8, TC 159, LDL 82, HDL 34, TG 215  
SCR and LFT’s WNL

Glitazones

Actos® and Avandia®

Glitazones: Things to Know

• Mechanism of Action:  
  – Reduce insulin resistance through stimulation of PPAR receptors  
  – Reduce hepatic glucose production  
• Maximal therapeutic effect in 6-12 weeks  
• Increase ovulation in pre-menopausal women  
  – Reduction in efficacy of birth control pills

Glitazones: Noteworthy Differences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Actos® mean % change</th>
<th>Avandia® mean % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>15.7·</td>
<td>23</td>
</tr>
<tr>
<td>HDL</td>
<td>14.9·</td>
<td>7.8</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>- 12·</td>
<td>13</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>8.8·</td>
<td>28.2</td>
</tr>
</tbody>
</table>

* = statistically significant
Glitazones: Additional Benefits
- Reduction of blood pressure
- Reduction of pro-thrombotic state
- Reduction of inflammatory cytokines
- Improvement in endothelial dysfunction

α-Glucosidase Inhibitors
- Precose® and Glyset®

α-Glucosidase Inhibitors
- **Mechanism of Action:**
  - Inhibits α-glucosidase enzyme in brush border of small intestine
  - Delays absorption of ingested complex carbohydrates
- **Efficacy:** ↓ A1c by 0.2 – 0.6%
- **Onset of action with first dose**

α-Glucosidase Inhibitors: Things to Know
- GI intolerance (90%)
  - Flatulence, diarrhea, abdominal pain, bloating
- Treat hypoglycemia with glucose tablets/gels or skim milk
- Monitor hepatic function with Precose®
- Contraindicated in pts with inflammatory bowel disease, colon ulceration & other bowel disorders, and cirrhosis
- Use with caution in patients with decreased renal function

Incretin Mimetic
- **Byetta®- Exenatide**
  - Approved for adjunctive therapy in patients with Type 2 Diabetes Mellitus who have inadequate glycemic control despite use of metformin and/or a sulfonylurea

Incretins
- Secreted from the mucosal cells in the small intestine
- Two major types:
  - GIP: glucose dependent insulinotropic polypeptide
  - GLP 1: glucagon like peptide
GLP-1

Food Consumption
Stomach

GLP-1 Release
Pancreas
Liver
Brain
Stomach

Insulin Release
Glucagon Release
Satiety
Gastric Emptying

Byetta®

Restores glucose dependent insulin release and prevents elevated post-prandial BG in Type 2 Diabetes

Byetta®: Clinical Trials

• Three 30 wk randomized, triple blind, multicenter, placebo controlled
• Intention to treat trials
• Phase III trials in patients with type 2 DM and suboptimal control
1. vs. placebo in pts already on metformin (n=336)
2. vs. placebo in pts already on SFU (n=377)
3. vs. placebo in pts on SFU/metformin (n=733)

Clinical Trial Results

A1c Reduction
• A1c reduction was significant regardless of baseline
• Increased A1c reduction with higher baseline value

Side Effects
• Nausea was the most common
• Declined with continued use

Hypoglycemia
• Increased risk with SU use
• No severe cases reported

Use and Storage

• Store unused and used Byetta® pens in the refrigerator.
• Protect from light. Do not freeze.
• In use Byetta® pens can only be used for 30 days.

Use and Storage

• SQ injection in thigh, abdomen, or upper arm
• Dosed BID within 60 minutes prior to morning and evening meals
• Initiated at 5mcg/dose and escalated to 10 mcg after 1 month of treatment
Byetta® should not be used in patients who...
- have a confirmed diagnosis of gastroparesis or are using medications that stimulate GI motility
- CrCl < 30ml/minute
- are pregnant or are at risk of becoming pregnant
- breastfeeding mothers
- are pediatric patients
- are hypersensitive to exenatide

Byetta® may reduce the effectiveness of medications requiring specific peak plasma levels following rapid absorption.

Case #4
- 66 y/o AA male
- Height: 6’0” Weight: 212lbs
- HPI: Type 2 DM, HTN, Hyperlipidemia
- Meds:
  - Glynase® 6 mg po ACB, Metformin 1000 mg BID, Actos® 45 mg qday, Lisinopril-HCT, Lipitor® 20, ASA, MVI
- Labs: A1c 7.4, TC 130, LDL 67, HDL 29, TG 170, LFTs and Scr WNL

Insulin
- Rapid Acting
  - Humalog®
  - NovoLog®
  - Apidra™
- Short Acting
  - Regular
  - Exubera®
- Intermediate
  - NPH
- Long Acting
  - Lantus®
  - Levemir®

Insulin Need

Basal Therapy
- NPH, Lantus®, or Levemir®
- Titrate to desirable FBG or hypoglycemia
- Continue sensitizers
- Continue secretagogue (BIDS Therapy)
**Treat to Target Study**

- Randomized, open multicentre trial
- 756 pts, Type 2 DM, overweight, A1c > 7.5
- HS Lantus® vs NPH titrated dose w/ existing oral therapy
- Outcomes: FPG, A1c, hypoglycemia, % pts reaching A1c < 7
- Duration: 24 weeks

**Treat To Target Algorithm**

<table>
<thead>
<tr>
<th>Mean of self monitored FPG from preceding two days</th>
<th>Increase in dose (units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 180 mg/dL</td>
<td>8</td>
</tr>
<tr>
<td>140 - 180 mg/dL</td>
<td>6</td>
</tr>
<tr>
<td>120 – 140 mg/dL</td>
<td>4</td>
</tr>
<tr>
<td>100 – 120 mg/dL</td>
<td>2</td>
</tr>
</tbody>
</table>

- Starting dose of 10 units HS w/ weekly adjustments
- No increase with BG < 72mg/dL in previous week
- Two-four unit ↓ with BG < 56mg/dL in previous week

**Treat to Target Findings**

- A1c reductions comparative between agents
- Increased incidence of hypoglycemia with NPH

**Bolus Therapy**

- Regular or Rapid Acting
- Titrate to 2hrPP BG or hypoglycemia
- Continue sensitizers
- Discontinue secretagogues

**Case #5**

54 y/o AAF

**Height:** 5'5”  **Weight:** 200lbs

**HPI:** Type 2 DM, HTN, Hyperlipidemia

**Meds:** Glucotrol® 10mg BID AC, Glucophage® 1000mg BID, Actos® 45mg qday, Lipitor® 80mg Qday, Altace® 5mg qday

**Labs:** A1c 9.6, TC 167, LDL 100, HDL 36, TG 154
Glucotrol®, Glucophage®, and Actos®
Lantus® 55 units

Symlin®- Pramlintide

- Virtually absent in Type 1 Diabetes
- Insufficient in Type 2 Diabetes
- Mechanism of Action
  - ↓ Glucagon secretion
  - ↓ Gastric emptying
  - ↑ Satiety
- Indication for Type 2 Diabetes: Adjunct therapy with mealtime insulin with or without use of oral agents
- Indication for Type 1 Diabetes: Adjunct therapy with mealtime insulin therapy, who have failed to achieve desired glucose control despite optimal insulin therapy
- Side Effects: Nausea and Headache

Symlin® Dosing

- **Initial Dose**
  - Type 1: 15mcg AC
  - Type 2: 60mcg AC
- **Max Dose**
  - Type 1: 60mcg AC
  - Type 2: 120mcg AC
- Meals to contain at least 250 calories and 30 grams CHO!
- Decrease pre-prandial insulin by 50%

| SYMLIN Dose Conversion | Parenteral Units | Draw the chloroethers
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>15mcg per dose</td>
<td>2.5 units</td>
<td></td>
</tr>
<tr>
<td>30mcg per dose</td>
<td>5 units</td>
<td></td>
</tr>
<tr>
<td>45mcg per dose</td>
<td>7.5 units</td>
<td></td>
</tr>
<tr>
<td>60mcg per dose</td>
<td>10 units</td>
<td></td>
</tr>
</tbody>
</table>

Note: 15mcg=2.5units!

Symlin® Dosing

- **Dosing**
  - SQ injection into thigh or abdomen only
  - Cannot be mixed with insulin
  - Injection site at least 2 inches from insulin site

Symlin®

- **Storage**
  - Unused vials should be kept refrigerated
  - Opened vials can be refrigerated or kept at room temperature.
  - Opened vials should be discarded after 28 days.
  - Discard frozen vials and those left above room temperature (>77°F).

Symlin® should not be used in patients who:
- have poor compliance with their insulin regimen
- have poor compliance with self-monitoring
- have A1C levels >9%
- have a history of recurrent severe hypoglycemia requiring assistance during the past 6 months
- have hypoglycemia unawareness
- have a confirmed diagnosis of gastroparesis or are using medications that stimulate GI motility
- Are pediatric patients

Symlin® may reduce the effectiveness of medications requiring specific peak plasma levels following rapid absorption.

Initiating Therapy
Add On Therapy

Things to Remember

- There is no right or wrong therapy when targeting the A1c, unless there are contraindications.
- Nutrition and exercise are always the best options.
- When adding therapy, figure out the source of the problem.
- When monitoring patterns, pay attention to lows first.
- Whenever possible, make therapy fix the lifestyle of the patient.