Achieving Optimal Control
In Type 2 Diabetes

Case Study

- 58 Year Old Journalist
- Type 2 DM Just Diagnosed
- HbA1C 7.3%
Natural History of Type 2 Diabetes

- Obesity
- IFG*
- Diabetes
- Uncontrolled Hyperglycemia

Glucose (mg/dL)

Relative Function (%)

- Fasting Glucose
- Post-meal Glucose
- Insulin Resistance
- Insulin Level

At Risk

β-Cell Failure

Years of Diabetes

*IFG=impaired fasting glucose.

Therapy of Diabetes

- Diet
- Exercise
- Medications
Natural History of Type 2 Diabetes

**Glucose (mg/dL)**

- Post-meal Glucose
- Fasting Glucose

**Relative Function (%)**

- Insulin Resistance
- Insulin Level

**Years of Diabetes**

*IFG=impaired fasting glucose.*

Major Targeted Sites of Drug Classes

- Pancreas
- Liver
- Gut
- Muscle and fat

**Hepatic glucose overproduction**

**Insulin resistance**

**Glucose Absorption**

**β-cell Dysfunction**

Sulfonylureas

Meglitinides

**Glucose level**

**Insulin Resistance**
### Therapeutic Options

#### Sulfonylureas

<table>
<thead>
<tr>
<th>Positives</th>
<th>Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Efficacious</td>
<td>- Hypoglycemia</td>
</tr>
<tr>
<td>- Long Experience</td>
<td>- Weight Gain</td>
</tr>
<tr>
<td>- Inexpensive</td>
<td>- Primary + Secondary Failure</td>
</tr>
</tbody>
</table>

#### Meglitinides

<table>
<thead>
<tr>
<th>Positives</th>
<th>Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Efficacious</td>
<td>- Hypoglycemia, Less Than SU</td>
</tr>
<tr>
<td>- Fairly Long Experience</td>
<td>- Weight Gain</td>
</tr>
<tr>
<td></td>
<td>- TID Dosing</td>
</tr>
<tr>
<td></td>
<td>- Expensive</td>
</tr>
</tbody>
</table>
GLP-1 Modes of Action in Humans

Upon Ingestion of Food...
- Stimulates Insulin Secretion
- Suppresses Glucagon
- Slows Gastric Emptying
- Reduces Food Intake

GLP-1 Is Secreted From the L-cells In the Intestine

This in Turn...

One More Point
Going Back to Those β Cells.....
**Natural History of Type 2 Diabetes**

*IFG=impaired fasting glucose.

**β-cell Neogenesis, Proliferation and Apoptosis**

- GLP-1 Stimulates Islet Neogenesis
- GLP-1 Inhibits Apoptosis
**Glucose Dependent Effects of GLP-1**

*Type 2 Diabetics (n=10)*

Mean (se) <p.05

---

**GLP-1 Effect : Blocked By DPP-4**

**Mixed Meal**
- Intestinal GLP-1 Secretion
  - GLP-1(7-36) Active
  - DPP-IV
  - GLP-1(9-36) Inactive
- Rapid Inactivation
- Renal Clearance

**Plasma**

**Deacon et al. Diabetes 1995; 44:1126**
GLP-1: Rapidly Degraded by DPP-4

Mentlein, R Regulatory Peptides 85:9-24, 1999

Secreted GLP-1 Rapidly Degraded

- GLP-1 (green) released into intestinal capillaries is immediately exposed to DPP-4 (red)¹
- >50% of secreted GLP-1 is already degraded before it reaches the general circulation²
- >40% of circulating GLP-1 is already degraded before it reaches β-cells²

¹Hansen L. et al. Endocrinology. 1999;140:5356-5363;
Enhance GLP-1 Effect By…

**GLP-1 AGENTS**

- Exenatide sc (Byetta)
- Liraglutide (Victoza) sc
- Albglutide sc

---

**GLP-1 Agents**

**The Good:**
- Decrease Post-Prandial Glucose
- No Hypoglycemia
- Potential For Weight Loss
- Perhaps β Cell Preservation

**The Not So Good:**
- GI Upset
- Injection
- Rare Reports Of Pancreatitis
- Cost
### Enhance GLP-1 Effect By...

#### GLP-1 AGENTS
- Exenatide sc (Byetta)
- Liraglutide sc (Victoza)
- Albglutide sc

#### DPP-4 INHIBITORS
- Sitagliptin (Januvia) po
- Saxagliptin (Onglyza) po
- Linagliptin (Tradjenta) po
- Vildagliptin (Galvus) po
- Alogliptin po

---

### DPP-4 Inhibitors

**The Good:**
- Decrease Post-Prandial Glucose
- No Hypoglycemia
- Weight Neutral
- Safe In Renal Disease
- No GI Upset
- Perhaps β Cell Preservation

**The Not So Good:**
- Short Experience
- Cost
**Therapeutic Options**

**Biguanide**

**Positives**
- Efficacious
- Long Experience
- Inexpensive
- Weight Loss

**Negatives**
- GI Upset
- Caution With Renal Disease
- Hold For Dye Procedures/Surgery

---

**Therapeutic Options**

**TZDs**

**Positives**
- Efficacious
- Reasonably Long Experience
- No Hypoglycemia
- β Cell Preservation

**Negatives**
- Increased CV Risk?
- Edema
- Weight Gain
- Fractures
TZD’s... Be Careful In Patients With CHF

Another TZD Concern ⇔

Increased Fractures In Women (Extra-Vertebral)
**Major Targeted Sites of Drug Classes**

- **Pancreas**
  - Decreased Glucose level
  - Sulfonlureas
  - Meglitinides
  - GLP-1 Agents
  - DPP 4 Inhibitors

- **Gut**
  - Glucosidase Inhibitors

- **Liver**
  - Hepatic glucose overproduction
  - Biguanides
  - TZDs

- **Muscle and fat**
  - Insulin resistance

**Therapeutic Options**

**α Glucosidase Inhibitors**

**Positives**
- Reasonably Long Experience
- No Hypoglycemia
- No Weight Gain

**Negatives**
- Only Mildly Efficacious
- GI Intolerance
New Oral Agents For Diabetes

Dopamine Receptor Agonists

Sodium-Glucose Transport Inhibitors (SGLT’s)

Low Dose Rapid Acting
Bromocriptine

- Dopamine Receptor Agonist (Cycloset)

- Increases Brain Dopamine To Reduce Insulin Resistance → Reduces Glucose, BP and Lipids

- Lowers A1C, BP and CV Risk
New Oral Agents For Diabetes

Sodium-Glucose Transport Inhibitors (SGLT’s)

Inhibit Sodium Glucose Co-transporter-2

↓

↓

Prevent Reabsorption Of Glucose In Renal Tubules

Therapeutic Progression

Combination Pills for Type 2 Diabetes

- Glyburide/Metformin (Glucovance)
- Glipizide/Metformin (Metaglip)
- Pioglitazone/Metformin (ActoPlusMet)
- Glimepiride/Pioglitazone (DuetAct)
- Sitagliptin/Metformin (Janumet)
- Saxaglitin/Metformin (Kombiglyze)

Case Study

- 58 Year Old Journalist
- Type 2 DM Just Diagnosed
- HbA1C 7.3%
- Metformin Started
Case Study

3 Months Later

- 58 Year Old Journalist
- Type 2 DM Just Diagnosed
- On Metformin
- Hb A1C 6.2%

Case Study

3 Years Later

- 61 Year Old Journalist
- Type 2 DM X 3 Years
- On Metformin
- Hb A1C 8.9%
Decisions, Decisions

- Failure On 1 Oral Agents
- Add 2nd Oral Agent
- Add GLP-1 Agent
- Add Insulin

Case Study

- 61 Year Old Journalist
- Type 2 DM X 3 Years
- On Metformin
- Hb A1C 8.9%
- Second Oral Agent Added
Case Study

3 Months Later

- 61 Year Old Journalist
- Type 2 DM x 3 Years
- On Metformin + Second Oral Agent
- Hb A1C 6.9%

Case Study

1 Year Later

- 62 Year Old Journalist
- Type 2 DM X 4 Years
- On Metformin + Second Oral Agent
- HbA1C 9.6%
What To Do If/When Two Oral Agents Are Not Enough?

Decisions, Decisions...

Failure On 2 Oral Agents

Add 3rd Oral Agent
Add GLP-1 Agent
Add Insulin
Physiologic Insulin Secretion:
Basal/Bolus Concept

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Basal Glucose</th>
<th>Prandial Glucose</th>
<th>Basal Insulin</th>
<th>Prandial Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.M.</td>
<td>150</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>P.M.</td>
<td>50</td>
<td>75</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>

A Basic Principle:
Fix The Fasting First
Currently Available Basal Insulins

- Neutral Protamine Hagedorn (1946)
- Insulin Glargine (2001)
- Insulin Detemir (2006)

Keep The Sulfonylurea, Tide, or The Gliptin On Board To Drive The β Cell For Mealtime Coverage!
Starting Basal Insulin

Continue Oral Agent(s) at Same Dosage
(Eventually Reduce)
Add Single Insulin Dose (~ 15 units)
  ✔ Glargine (Anytime)
  ✔ Increase Insulin Dose 1 unit Daily Until
    FBS<100mg &/or HbA1C < 7%
Case Study

- 62 Year Old Journalist
- Type 2 DM x 4 Years
- On Metformin + Second Oral Agent
- Hb A1C 9.6%
- Basal Insulin Added

4 Months Later

- 62 Year Old Journalist
- Type 2 DM X 4 Years
- On Metformin + Second Oral Agent + Basal Insulin
- Hb A1C 6.9%
Case Study
2 Years Later

- 64 Year Old Journalist
- Type 2 DM x 7 Years
- On Metformin + Second Oral Agent + Basal Insulin
- HbA1C 7.8% With Fasting Sugars Between 100 and 110 mg%

What’s Going On?

Postprandial Glucose Must Be Elevated
BOLUS INSULIN...

Currently Available Bolus Insulins

- Regular (1921)
- Insulin Lispro (1996)
- Insulin Aspart (2000)
- Insulin Glulisine (2006)
**Insulin Profiles**

- Aspart, Lispro, Glulisine
- Regular

Plasma Insulin Levels vs. Time (hr)

- Rule Of Thumb For Glargine:
  - 50% Basal
  - 50% Prandial, Divided Over 3 Meals

**Bolus Insulin**

- Add Rapid Acting Insulin For Mealtime Coverage

Rosenstock J. Clin Cornerstone. 2001;4:50
Glucose Patterns in Type 2 Diabetes Mellitus

Continue SU/Tide/DPP-4 Inhibitor, Metformin, TZD

Case Study
3 Months Later

- 64 Year Old Journalist
- Type 2 DM x 7 Years
- On Metformin + Second Oral Agent + Basal Insulin + 1 Shot Bolus Insulin
- HbA1C 6.7%
**Case Study**

2 Years Later

- 66 Year Old Journalist
- Type 2 DM X 9 Years
- On Metformin + Second Oral Agent + Basal Insulin + 1 Shot Bolus Insulin
- Hb A1C 9.8%

**Glucose Patterns in Type 2 Diabetes Mellitus**

*Discontinue SU/Tide/DPP-4 Inhibitor; Continue Metformin, TZD*
Fine Tuning The Bolus

The Bolus Has 2 Components:

- **Prandial**
- Fine Tune By Carbohydrate Counting
- **Correction Factor**
- Adjustment For Pre-Meal Hyperglycemia

Case Study

- 66 Year Old Journalist
- Type 2 DM x 9 Years
- On Metformin + Second Oral Agent* + Basal Insulin + Bolus Insulin Before Each Meal
- HbA1C 6.9%

*If 2nd oral agent is SU, it should be discontinued.