A New Therapeutic Strategy for Type 2 Diabetes

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Overview

• Underlying defects with Type 2 diabetes
• Importance of managing postprandial glucose control
• Incretin Hormones
  – New therapies that target incretin hormones
The Diabetes Epidemic

- 8.0% of US children and adults have diabetes.
- 57 million have pre-diabetes.
- 1.6 million new cases diagnosed in people aged 20 years or older in 2007.
- 90-95% Type 2

Normal Glucose Homeostasis

- Glucose output
- Glucose uptake
- Blood glucose

Fasting State

Glucagon (alpha cell)
Insulin (beta cell)
Pancreas

Liver
Muscle
Adipose tissue

Normal Glucose Homeostasis

Blood glucose

Glucagon (alpha cell)

Insulin (beta cell)

Pancreas

Glucose output

Fed state

Glucose uptake

Liver

Muscle

Adipose tissue

Case Study

- Susan is a 47-year-old Native American woman who signs up for glucose screening in your pharmacy.
- Medical History: gestational diabetes 13 yrs ago with only child, hypertension.
- Medications: HCTZ 25 mg qd.
- Family History: 62-year-old father developed type 2 diabetes at age 50.
- Fasting glucose = 105 mg/dl.
- HT: 5'6”, WT: 188 lbs (BMI: 30.3).
- BP: 142/86 mm Hg.
Natural History of Type 2 Diabetes

IGT=impaired glucose tolerance; IFG=impaired fasting glucose.

**Major Pathophysiologic Defects**

- Insulin resistance
- Glucose uptake
- Hepatic glucose output
- Glucagon (alpha cell)
- Insulin (beta cell)
- Islet-cell dysfunction
- Insulin resistance
- Glucose uptake
- Muscle
- Adipose tissue

**Hyperglycemia**

- Liver

**Sources:**
Other fundamental defects in Type 2 diabetes

- Accelerated gastric emptying
- Impaired meal-stimulated insulin release (deficient amylin and GLP-1 secretion)
Gastric Emptying Rates


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Type 2 Diabetes: A Disease of Deficient Appetite Signals?

- B-cell defect
- Reduced neuronal insulin/leptin action
- Reduced GLP-1 and amylin
- Positive energy balance
- Food intake
- Energy expenditure

Type 2 Diabetes

Insulin Resistance

Unmet Pathophysiologic Needs in Type 2 Diabetes Mellitus

- Progressive loss of beta-cell function and mass
- Inappropriate glucagon secretion
- Uncontrolled postprandial hyperglycemia
- Possible impaired satiety signals resulting in weight gain
- Accelerated gastric emptying
- Deficient incretin effect
Case Study

• Based on her risk for Type 2 diabetes and elevated fasting level, Susan was referred to her PCP
• Lab results:
  – 2-hour postmeal glucose = 158 mg/dL
• Consultation with dietitian
• Starts lifestyle modification program (weight loss and walking 30 mins 3x/wk)
# Current Treatment Guidelines

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Normal</th>
<th>ADA Goal</th>
<th>ACE/AACE Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting/preprandial plasma glucose (mg/dl)</td>
<td>&lt;100</td>
<td>70-130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mg/dl)</td>
<td>&lt;120</td>
<td>&lt;180</td>
<td>&lt;140</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>≤6.5</td>
</tr>
</tbody>
</table>

ADA = American Diabetes Association  
ACE/AACE = American College of Endocrinology/American Association of Clinical Endocrinologists  
*Diabetes Care* 2008;31:S12-S54.  
Recent Trials in Type 2 DM

- **ACCORD**
  - median 8 yrs of disease, target A1C <6%, 3.4 yr trial
  - median A1C 6.4% vs 7.5%
  - Increased risk of death from any cause and death from CV
  - 28% gained more than 22 lbs

- **ADVANCE**
  - mean 10 yrs of disease, target A1C ≤6.5%, 5 yr trial
  - median A1C 6.4 vs 7.0
  - reduced new onset microalbuminuria & nephropathy

What is A1C and Why is it Important?

- Glycated or glycosylated hemoglobin
  - HbA1C, A1C
- Normal range: 4.0% to 6.7%
- Reflects mean glucose levels over preceding 120 days
- Elevated in: Uncontrolled diabetes mellitus, lead toxicity, alcoholism, iron deficiency anemia, hypertriglyceridemia
### Mean Plasma Glucose

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mean plasma glucose mg/dl</th>
<th>Mean plasma glucose mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>135</td>
<td>7.5</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
<td>9.5</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
<td>11.5</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>13.5</td>
</tr>
<tr>
<td>10</td>
<td>275</td>
<td>15.5</td>
</tr>
<tr>
<td>11</td>
<td>310</td>
<td>17.5</td>
</tr>
</tbody>
</table>

*Diabetes Care 2008;31:S12-S54*
GOOD GLYCEMIC CONTROL: A CRITICAL GOAL

- Each 1% reduction in mean A1C
  - Reduces risk of death from diabetes by 21%
  - Reduces risk of microvascular complications by 37%

A1C Goal Achievement

- > 7% (36%)
- < 7% (64%)

UKPDS 35 BMJ 2000:321:405-412
GOOD GLYCEMIC CONTROL: A CRITICAL BUT ELUSIVE GOAL

Multiple factors continue to challenge goal achievement.

– natural progression of beta-cell dysfunction with increasing hyperglycemia
– Poor adherence to prescribed therapy
– Uncontrolled post-prandial glucose
– Poor adherence to prescribed therapy
– Uncontrolled post-prandial glucose
Increasing Contribution of PPG as A1C Improves

FPG = fasting plasma glucose
PPG = post prandial glucose

Diabetes Care 2003;26:881-885.
Patients With Type 2 Diabetes May Spend 12 Hours per Day in the Postprandial State

Duration of Postprandial State

- Postprandial
- Postabsorptive
- Fasting

Times of blood sampling to obtain a diurnal blood glucose profile

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Importance of Postprandial Hyperglycemia

- IGT is a risk factor for cardiovascular disease
- Contributes more to A1C than FPG at A1Cs < 7.3%
- Can be rate limiting factor for achieving adequate glycemic control

*Diabetologia* 2002;45:1224-1230
*Diabetes Care* 1999;22:920-924
Incretin Hormones

- Peptides produced by GI tract in response to food
- Influence post-prandial insulin release (insulinotropic)
- Glucagon-like peptide-1 (GLP-1)
- Gastric inhibitory polypeptide (GIP)
The Incretin Effect – Beta Cell Response to Oral Glucose

GLP-1 Actions in Humans

Upon ingestion of food
GLP-1 is secreted from the L cells in the intestine

• Stimulates glucose dependent insulin secretion
• Suppresses glucagon secretion
• Slows gastric emptying
• Reduces food intake
• Improves insulin sensitivity

Long term effects (in animals)
• Increases beta cell mass and maintains beta-cell efficiency
Postprandial GLP-1 Levels

NGT = normal glucose tolerance
IGT = impaired glucose tolerance
T2DM = type 2 diabetes mellitus

Dipeptidyl Peptidase IV (DPP-IV)

- Lymphocyte cell surface protein CD26
- Enzyme that rapidly inactivates GLP-1
- Inhibition of DPP-IV enhances activity of GLP-1 and other bioactive peptides (GIP, PACAP38, GRP)
  - Stimulates release of insulin
  - Reduces secretion of glucagon
Incretin-Based Therapies

• Incretin Mimetics (GLP-1 agonists/analogs)
  – Exenatide (Byetta)
  – Others: Liraglutide, LY307161 SR, CJC-1131, ZP10, BIM51077

• Incretin Enhancers (DPP-IV inhibitors)
  – Sitagliptin
  – Vildagliptin
  – Others: saxagliptin
Exenatide (Byetta®)

- Binds to GLP-1 receptor
- T1/2 ~ 2.5 hrs
- Given as 5 – 10 mcg SC within 1 hr before morning and evening meal
- Indicated for type 2 patients not controlled on metformin, sulfonylurea, TZD, or combination
- Long acting formulation under development
Exenatide (Byetta®)

What to Do About Nausea?

• Adverse effects
  – Nausea (50%), diarrhea, dyspepsia, pancreatitis (rare)
• Tends to improve over time
• May be less severe if exenatide is given closer to a meal
• Low-fat diet and eating slowly seem to help
• Remind patient to stop eating when full
Exenatide 3 year A1C Data

N = 217

Buse JB, et al. Presented at ADA, 67th Scientific Sessions; 2007; Chicago, IL (abstract 0283-OR)
No diet and exercise regimen was provided; 

N = 217; Mean (- SE); \( P<0.0001 \) from baseline to 3 years and between 30 weeks and 3 years 

Buse JB, et al. Presented at ADA, 67th Scientific Sessions; 2007; Chicago, IL (abstract 0283-OR)
Patients received MET or SFU; n = 92.

Mean (+ SE); \( P < 0.0001 \) from baseline after 3 years of exenatide

Buse JB, et al. Presented at ADA, 67th Scientific Sessions; 2007; Chicago, IL (abstract 0283-OR)

**Improvement in HOMA-B From Baseline Through 3 Years**

\( P < 0.0001 \)

！[](chart.png)
Exenatide

• Advantages
  – Does not cause hypoglycemia unless combined with unadjusted doses of other hypoglycemics
  – Weight loss of ~ 4-6 lbs over 6 months, > 10 lbs over 2 years
  – Decreases A1C by 0.5-1%
  – Longer term A1C, weight, and HOMA-B data

• Disadvantages
  – ADE: diarrhea, dyspepsia, nausea, vomiting
  – Injection administration only
  – Administer within 60 minutes before meals
  – Concurrent use with insulin, meglitinides, or α-glucosidase is not well studied
Sitagliptin (Januvia®)

- Orally active, selective inhibitor for the DPP-IV enzyme
- T1/2 ~ 12.4 hrs
- A1C effect: ↓ 0.65 - 0.8%
- Oral dosing: 50 - 100 mg once daily
- Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
- Can be used in combination - PI notes it has not been studied with insulin
In Combination with Metformin

Diabetes Obes Metab. 2007;9(2):186-93.
## Dosage

- **Normal renal function or mild dysfunction**
  - 100 mg daily

- **Moderate to severe renal insufficiency**

<table>
<thead>
<tr>
<th>CrCl ≥30 to &lt;50 mL/min (~Serum Cr levels [mg/dL])</th>
<th>50 mg once daily</th>
<th>25 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>May be switched to 25 mg once daily.</td>
<td></td>
</tr>
<tr>
<td>Severe and ESRD‡</td>
<td></td>
<td>CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(~Serum Cr levels [mg/dL])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men: &gt;3.0; Women: &gt;2.5</td>
</tr>
</tbody>
</table>

#### Drug Interactions

- No known clinically meaningful drug interactions

‡ESRD = end-stage renal disease requiring hemodialysis or peritoneal dialysis.
Sitagliptin

- **Adverse Effects**
  - Premarketing – equal to placebo
  - Sitagliptin 100 mg versus placebo
    - Hypoglycemia (1.2% vs 0.9%)
    - Abdominal pain (2.3%, 2.1%)
    - Nausea (1.4%, 0.6%)
    - Diarrhea (3.0%, 2.3%)
  - Postmarketing
    - anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome
**Sitagliptin**

- **Advantages**
  - No known drug interactions
  - Studied as monotherapy and in combination with glitazones, glipizide, and metformin
  - Available in combination with metformin (Janumet®)
    - 50mg/500mg & 50/1000
  - Weight neutral
  - Low rate of side effects
  - Low risk of hypoglycemia

- **Disadvantages**
  - Concurrent use with insulin & meglitinides not well studied
Vildagliptin (Galvus®)

- Indication: ? Most likely will be similar to sitagliptin
- A1C effect: ↓ 0.5 - 0.8%
- Oral dosing: 50mg qd or bid
- Adverse effects: ? similar to placebo
- Skin toxicity worries have put back approval in U.S
- Approved in 50 mg and 100 mg (50 mg bid) doses by the European Union in September 2007 in combination with metformin, TZD or SU
- Liver safety problems with the higher dose

Greatest Potential Limitation of DPP-IV Inhibitors

- DPP-IV is ubiquitous
- Nonspecific inhibition may increase neuropeptide Y, endomorphin peptide YY, growth hormone-releasing hormone, glucagon-like peptide 2, and other chemokines
- Effect on immune system appears positive or neutral
GLP-1 Mimetics versus DPP-IV Inhibitors

- No head-to-head comparisons
- Injectable vs. oral
- BID vs. QD
- Greater risk of hypoglycemia with mimetics
- More weight loss with mimetics
- DPP-IV agents appear better tolerated (less nausea)
- Similar impact on A1C
Incretin Agents

- Restore glucose-dependent insulin secretion in face of ingested nutrients
- Suppress glucagon levels to restore appropriate balance
- Potential to preserve beta cell function
Who might benefit most from incretin based therapy?

- Overweight or obese patient
  - rather than add an agent which may cause additional weight gain
- Uncontrolled on current therapy
  - Especially those close to A1C goal
- Elderly or frail
- ? Early in disease to preserve beta cells
Effects in IGT

- 179 subjects with IGT (2-h glucose 9.1 mmol/l, A1C 5.9%)
- Vildagliptin 50 mg qd vs. placebo
- ↑ GLP-1, GIP & ↓ glucagon
- 32% reduction in postprandial glucose excursions
- ↑ β cell function
- No hypoglycemia or weight gain
Case Study

- Susan is now on
  - glyburide 10 mg bid
  - metformin 1000 mg bid
- A1C = 7.2%
- She lost 10 lbs with lifestyle changes but has regained this plus another 5 lbs since on glyburide.
To Sum It All Up

- Incretin hormones have important role in Type 2 disease and management
- Incretin agents stimulate glucose dependent insulin secretion, slow gastric emptying, suppress postprandial glucagon levels, and decrease liver glucose release
- Agents are agonists or DPP-IV inhibitors
- Exenatide and sitagliptin on market
- Similar efficacy and side effect profile in Phase III testing of gliptins
- Many more incretin agents are waiting in the wings