Update on Diabetes Mellitus Treatment: Targeting the Incretin System
Overview

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

• 7.0% of US children and adults have diabetes.
• 54 million have pre-diabetes
• 1.5 million new cases diagnosed in people aged 20 years or older in 2005.
• 90-95% Type 2

Prevalence of Diagnosed Diabetes in the U.S., 2001

JAMA 2003;289(1):76-9
Insulin and Glucagon Regulate Normal Glucose Homeostasis

- **Glucagon (alpha cell)**
- **Insulin (beta cell)**

**Fasting State**

**Glucose output**

**Blood glucose**

**Glucose uptake**

- Liver
- Muscle
- Adipose tissue

Insulin and Glucagon Regulate Normal Glucose Homeostasis

- Glucagon (alpha cell)
- Insulin (beta cell)

Fed state

- Pancreas
- Liver
- Muscle
- Adipose tissue

Glucose output

Blood glucose

Glucose uptake

Case Study

• June is 47-year-old woman who signs up for glucose screening in your pharmacy.
• Medical History: gestational diabetes 13 yrs ago with only child, hypothyroidism, occasional vaginal yeast infections
• Medications: levothyroxine 0.1 mcg/day
• Family History: 70-year-old father developed type 2 diabetes at age 58
• 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.

What are the fundamental defects in Type 2 diabetes?

- Relative lack of insulin
  - Early in disease → insulin resistance
  - Later → combination of insulin resistance and declining insulin secretion
  - Late → failure of beta cells

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

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, June was referred to her PCP

• Lab results:
  – 2-hour postmeal glucose = 158 mg/dL

• Consultation with dietician

• 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>
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<tbody>
<tr>
<td>Fasting/preprandial plasma glucose</td>
<td>&lt; 100</td>
<td>90-130</td>
<td>≤ 110</td>
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<tr>
<td>(mg/dl)</td>
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<td></td>
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<tr>
<td>Postprandial plasma glucose</td>
<td>&lt; 140</td>
<td>&lt; 180</td>
<td>≤ 140</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
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<tr>
<td>A1C (%)</td>
<td>&lt; 6</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
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ADA = American Diabetes Association  
ACE/AACE = American College of Endocrinology/American Association of Clinical Endocrinologists  

*Diabetes Care* 2006;29(suppl 1):S4-S42.  
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
GOOD GLYCEMIC CONTROL: A CRITICAL BUT ELUSIVE GOAL

- Elevated A1C risk factor for CV disease
- Every percentage-point ↓ in A1C reduced the risk of microvascular complications by 25% to 37% (UKPDS).

Lancet 1998;352:837-853
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
  – lack of long-term success with diet and exercise
  – poor adherence to prescribed therapy
  – uncontrolled post-prandial glucose
Both FPG and PPG Contribute to Elevated A1C Levels

Plasma glucose mg/dL

0 100 200 300
0600 1200 1800 2400 0600

24-Hour Glucose

Postprandial hyperglycemia
Fasting hyperglycemia
Normal glucose

Increasing Contribution of PPG as A1C Improves

FPG = fasting plasma glucose
PPG = post prandial glucose

Diabetes Care 2003;26:881-885.
Relationship between A1C Baseline and Reduction With Pharmacologic Intervention

Baseline A1C% 6.0–6.9 7.0–7.9 8.0–8.9 9.0–9.9 10.0–11.8
Number of patients enrolled in clinical trials

<table>
<thead>
<tr>
<th>Baseline A1C%</th>
<th>6.0–6.9</th>
<th>7.0–7.9</th>
<th>8.0–8.9</th>
<th>9.0–9.9</th>
<th>10.0–11.8</th>
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<td>n=5,269</td>
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<td>n=266</td>
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</table>

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
## Treatments for Type 2 Diabetes

### Increase insulin responsiveness
- **Biguanides**
  - Metformin (Glucophage®, Fortamet®)
- **Thiazolidinediones**
  - Rosiglitazone (Avandia®)
  - Pioglitazone (Actos®)

### Stimulate insulin release
- **Sulfonylureas**
  - Glipizide (Glucotrol®, glipizide XL (Glucotrol XL®))
  - Glyburide (DiaBeta®, Glynase®, Micronase®)
- **Meglitinides**
  - Nateglinide (Starlix®)
  - Repaglinide (Prandin®)

### Modify intestinal absorption of carbohydrate
- **Alpha-glucosidase inhibitor**
  - Acarbose (Precose®)
  - Miglitol (Glyset®)

### Reduce postprandial glucose
- **Amylin Analog**
  - Pramlintide (Symlin®)
- **Incretin mimetics**
  - Exenatide (Byetta®)
  - Sitagliptin (Januvia®)
  - Vildagliptin (Galvus®)

### Correct Insulin Deficiency
- **Insulin**
Amylin

- Works in conjunction with insulin to help control blood glucose levels
- A neuroendocrine hormone that is cosecreted by the beta cells of the pancreas in response to food intake.
- Regulates glucose appearance in the bloodstream from the stomach and liver.
Pramlintide (Symlin®)

• Synthetic analog of human amylin for postprandial control of glucose
• Slows gastric emptying, suppresses postprandial glucagon secretion and modulates appetite by enhancing satiety
• Indicated in Type 2 diabetes
  – adjunct treatment to mealtime insulin with or without a concurrent sulfonylurea agent and/or metformin
Pramlintide (Symlin®)

• Given SC with major meals
• Advantage
  – Weight loss of ~1-1.5 kg over 6 months
  – Decreases HbA1c by 0.5-0.7%
• Disadvantage
  – ADE: hypoglycemia, nausea (50%), headache
  – Contraindication: gastroparesis
  – Slows the absorption of oral medications
• Important to lower mealtime insulin dose 50% when start this agent
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 Secretion and Metabolism

Mixed Meal
Intestinal GLP-1 release

GLP-1 (7-36)
Active

DPP-IV
Rapid Inactivation (>80% of pool)

GLP-1 (9-36)
Inactive

Renal Clearance

GLP-1 Actions

DPP = dipeptidyl peptidase
GLP-1 Actions

- Stimulates glucose dependent insulin secretion
- Slows gastric emptying
- Suppresses postprandial glucagon secretion
- Reduces food intake
- May improve insulin sensitivity
- *In vitro* stimulates beta-cell proliferation
Postprandial GLP-1 Levels

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

J Clin Endocrinol Metab. 2001;86(8):3853-60.
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
GLP-1 Secretion and Metabolism

Mixed Meal
Intestinal GLP-1 release
GLP-1 (7-36) Active
DPP-IV
GLP-1 (9-36) Inactive
Plasma
Renal Clearance

DPP = dipeptidyl peptidase
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, or combination
- Long acting formulation under development
Effects of Exenatide on Postprandial Glucose

J Clin Endocrinol Metab 2003;88:3082-3089
Exenatide

• Drug Interactions
  – Take oral contraceptives and antibiotics 1 hr before
  – ? take all medications 1 hr before or with meal when drug is not given

• Adverse effects
  – Nausea (50%), diarrhea, dyspepsia
  – Hypoglycemia can occur when given with sulfonylureas
What to Do About Nausea?

• 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

• Advantages
  – Does not caused 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%

• Disadvantages
  – ADE: diarrhea, dyspepsia, nausea, vomiting
  – Injection administration only
  – Administer within 60 minutes before meals
  – Concurrent use with insulin, TZD, meglitinides, or α-glucosidase is not well studied
Investigational GLP-1 Analogues

• Liraglutide
  – Long-acting, acylated GLP-1 analogue
  – $t_{1/2} \sim 12-14$ hrs
  – Once daily SC injection
  – Modest weight loss
A1C Reduction with Liraglutide

Placebo adjusted Δ in A1C (%)

-0.9
-0.7
-0.5
-0.3
-0.1
0

Liraglutide 0.6 mg (N=30)
Liraglutide 0.75 mg (N=28)
Glimepiride (N=26)

* P < 0.001 vs placebo

Diabetes Care 2004;27:1335-1342
Sitagliptin (Januvia®)

• Orally active, selective inhibitor for the DPP-4 enzyme
• T1/2 ~ 12.4 hrs
• A1C effect: ↓ 0.65 - 0.8%
• Oral dosing: 50 - 100 mg once daily
  – can be administered with or without food
Placebo-Adjusted Results in a 24-Week Study of Sitagliptin

**A1C**
Mean Baseline: 8.0%
P<0.001*
Change in A1C, %
-0.8†
(95% CI: −1.0, −0.6)
n = 229

**FPG**
Mean Baseline: 170 mg/dL
P<0.001*
Change in FPG, mg/dL
-17†
(95% CI: −24, −10)
n = 234

**2-hr PPG**
Mean Baseline: 257 mg/dL
P<0.001*
Change in 2-hr PPG, mg/dL
-47†
(95% CI: −59, −34)
n = 201

*Compared with placebo.
†Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡Difference from placebo.
Sitagliptin Indications

• Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

• To improve glycemic control in combination with metformin or a PPARγ agonist (eg, thiazolidinediones) when the single agent alone with diet and exercise does not provide adequate glycemic control

• Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis
# Dosage

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

- **Moderate to severe renal insufficiency**

<table>
<thead>
<tr>
<th></th>
<th>50 mg once daily</th>
<th>25 mg once daily</th>
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<tbody>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥30 to &lt;50 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(~Serum Cr levels [mg/dL])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men: &gt;1.7–≤3.0; Women: &gt;1.5–≤2.5)</td>
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<td></td>
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</tbody>
</table>

|                        |                  |                  |
| **Severe and ESRD‡**   |                  |                  |
| CrCl <30 mL/min        |                  |                  |
| (~Serum Cr levels [mg/dL]) |                  |                  |
| Men: >3.0; Women: >2.5) |                  |                  |

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

• Drug Interactions
  – No known clinically meaningful drug interactions
  – Based on in vitro data, sitagliptin does not inhibit CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6 or induce CYP3A4
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%)
Sitagliptin

• Advantages
  – No known drug interactions
  – Studied as monotherapy and in combination with glitazones, glipizide, and metformin
  – Weight neutral
  – Low rate of side effects
  – Low risk of hypoglycemia

• Disadvantages
  – Concurrent use with insulin, meglitinides, or α-glucosidase is not well studied
Vildagliptin (Galvus®)

- Indication: Most likely will be similar to sitagliptin
- A1C effect: ↓ 0.5 - 0.8%
- Oral dosing: 50-100 mg once daily
- Adverse effects: similar to placebo
- Effect on weight: 0 → -1.5 kg
- No known drug interactions
- Studied as monotherapy and in combination with glitazones, glimepiride, metformin, and insulin

A1C Reduction with Vildagliptin

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Δ A1C (%)</th>
</tr>
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<tbody>
<tr>
<td>Placebo (n=55)</td>
<td>-0.13%</td>
</tr>
<tr>
<td>Vildagliptin 50 mg</td>
<td>-0.56%</td>
</tr>
<tr>
<td>Vildagliptin 100 mg</td>
<td>-0.53%</td>
</tr>
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</table>

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
GLP-1 Mimetics versus DPP-IV Inhibitors

- No head-to-head comparisons
- Injectable vs. oral
- BID vs. QD
- Greater risk of hypoglycemia with mimetics
- Better 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

• ? Early in disease to preserve beta cells
Case Study

- June 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.
Dual Alpha-Gamma PPAR Agonists

- PPAR
  - Proliferator-Activated Receptor
  - Members of the larger steroid hormone nuclear receptor family
- Thiazolidinediones → PPAR-gamma agonists
- Fibrates → PPAR-alpha agonists
- Alpha/gamma agonists → lipid lowering and insulin sensitizing effects
Dual PPAR Agonists

• Development stopped
  – muraglitazar (Pargluva)
  – farglitazar
  – tesaglitazar (Galida)
  – ragaglitazar
  – TAK 559

• Still in the pipeline
  – GSK 590735, 501516, 677954
  – TAK 654
  – AZD6610
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 glucoseagon 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