Modulating the Incretin System: 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

- 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 Overweight in the U.S., 2006

Prevalence of Diabetes in the U.S., 2005

Normal Glucose Homeostasis

Normal Glucose Homeostasis

Blood glucose

Glucose output

Glucose uptake

Pancreas

Fed state

Glucagon (alpha cell)

Insulin (beta cell)

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

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


Clinical outcomes have altered the definition of abnormal glucose metabolism.

Relative Function

Glucose

Years from Diabetes Diagnosis

-10 -5 0 5 10 15 20 25 30

Pregnancy

Postprandial glucose

Fasting glucose

Insulin resistance — hepatic and peripheral

Beta-cell function

Natural History of Type 2 Diabetes

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
- Impaired meal-stimulated insulin release (deficient amylin and GLP-1 secretion)
- Unsuppressed postprandial glucagon secretion

Gastric Emptying Rates

Type 2 Diabetes: A Disease of Deficient Appetite Signals?

- Type 2 Diabetes
- Insulin Resistance
- Reduced neuronal insulin/leptin action
- B-cell defect
- Reduced GLP-1 and amylin
- Positive energy balance
- Food intake
- Energy expenditure

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 ADA Goal</th>
<th>ACE/AACE Goal</th>
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</thead>
<tbody>
<tr>
<td>Fasting/preprandial plasma glucose (mg/dL)</td>
<td>&lt; 100</td>
<td>70-130</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mg/dL)</td>
<td>&lt; 120</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>&lt; 6</td>
<td>&lt; 7</td>
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</tbody>
</table>

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>mmol/l</th>
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<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>
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</tbody>
</table>
GOOD GLYCEMIC CONTROL: A CRITICAL GOAL

- Each 1% reduction in mean A1C
  - Reduces risk of death from diabetes by 21%
  - Reduces risk of heart attack by 14%
  - Reduces risk of microvascular complications by 37%

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

GOOD GLYCEMIC CONTROL: A CRITICAL BUT ELUSIVE GOAL

- Lack of long-term success with diet and exercise
- Poor adherence to prescribed therapy
- Uncontrolled post-prandial glucose

GOOD GLYCEMIC CONTROL: A CRITICAL BUT ELUSIVE GOAL

Both FPG and PPG Contribute to Elevated A1C Levels


Increasing Contribution of PPG as A1C Improves

FPF = 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

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<thead>
<tr>
<th></th>
<th>Duration</th>
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<tbody>
<tr>
<td>Breakfast</td>
<td>4 AM</td>
</tr>
<tr>
<td>Lunch</td>
<td>Midnight</td>
</tr>
<tr>
<td>Dinner</td>
<td>8 AM</td>
</tr>
</tbody>
</table>

Why Care about Postprandial Hyperglycemia?

- 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)

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

Treatments for Type 2

- Increase insulin responsiveness
  - Sulfonylureas
    - Glipizide (Glucotrol®), glipizide XL (Glucotrol XL®)
    - Glyburide (DiaBeta®, Glynase®, Micronase®)
    - Glimepiride (Amaryl®)
  - Meglitinides
    - Nateglinide (Starlix®)
    - Repaglinide (Prandin®)
- Moderate intestinal absorption of carbohydrate
  - Alpha-glucosidase inhibitors
    - Acarbose (Precose®)
    - Miglitol (Glyset®)
- Reduce postprandial glucose
  - Amylin analog
    - Exenatide (Byetta®)
  - Incretin mimetics
    - Tanagliptin (Januvia®)
    - Vildagliptin (Galvus®)
- Correct insulin deficiency
  - Insulin
-Modify intestinal absorption of carbohydrates
  - Alpha-glucosidase inhibitor
  - Acarbose (Precose®)
  - Miglitol (Glyset®)

The Incretin Effect – Beta Cell Response to Oral Glucose

- Plasma Glucose (mg/dL)
- C-peptide (nmol/L)

Increase Glucose

Insulin

Incretin Effect
**GLP-1 Secretion and Metabolism**

- **Mixed Meal**
  - Intestinal GLP-1 release
  - GLP-1 (7-36) Active
  - DPP-IV Inactive
  - Rapid inactivation (>80% of pool)
  - Renal Clearance

**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

**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/analog)
  - 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

- 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 3 year A1C Data

- Baseline A1C 8.2%
- Change in A1C: -1.1 ± 0.1%
- % achieving A1C ≤ 7%: 46%

Continued Weight Reduction at 3 years

- Baseline Weight: 99 kg
- Change in body weight: -5.3 ± 0.4 kg
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)

**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 0.3-1%
  - 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, megalinides, or \( \alpha \)-glucosidase is not well studied

**Investigational GLP-1 Analogues**

- **Liraglutide**
  - Long-acting, acylated GLP-1 analogue
  - \( t_{1/2} \) ~ 12-14 hrs
  - Once daily SC injection
  - Modest weight loss

**Sitagliptin (Januvia®)**

- Orally active, selective inhibitor for the DPP-IV enzyme
- \( T_{1/2} \) ~ 12.4 hrs
- A1C effect: \( \downarrow \) 0.65 - 0.8%
- Oral dosing: 50 - 100 mg once daily
  - can be administered with or without food

**A1C Reduction with Liraglutide**

- Placebo-adjusted \( \Delta \) in A1C (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>A1C Reduction (Placebo Adjusted) (%)</th>
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<tbody>
<tr>
<td>Liraglutide 0.6 mg (N=20)</td>
<td>-0.8</td>
</tr>
<tr>
<td>Liraglutide 0.75 mg (N=25)</td>
<td>-1.0</td>
</tr>
<tr>
<td>Glimepiride (N=26)</td>
<td>-0.8</td>
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\( * P<0.001 \) vs placebo

<table>
<thead>
<tr>
<th>Group</th>
<th>A1C Reduction (Placebo Adjusted) (%)</th>
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<tbody>
<tr>
<td>Placebo-Adjusted Results in a 24-Week Study of Sitagliptin</td>
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<tr>
<th>A1C</th>
<th>Mean Baseline: -0.5%</th>
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<tr>
<td>Placebo-Adjusted</td>
<td>Mean Baseline: -1%</td>
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\( * P=0.031 \) Compared with placebo

\( \Delta \) from prior antihyperglycemic therapy status and baseline value

\( \Delta \) from placebo

Data from package insert
**Sitagliptin Indications**

- 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

**Dosage**

- Normal renal function or mild dysfunction
  - 100 mg daily
- Moderate to severe renal insufficiency
  - 50 mg once daily
  - 25 mg once daily

**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**

- 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

**Sitagliptin**

- Adverse Effects
  - Premarketing – equal to placebo
  - Sitagliptin 100 mg versus placebo
    - Hypoglycemia (2.2% 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
**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
- Effect on weight: 0 → -1.5 kg
- No known drug interactions
- Studied as monotherapy and in combination with glitazones, glimepiride, metformin, and insulin

**Update on Vildagliptin**
- 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

*May I be excused? My brain is full.*