Managing Postprandial Glucose

Mary Lynn McPherson, Pharm.D., BCPS
Professor, University of Maryland School of Pharmacy

This program has been supported by an educational grant from Bristol-Myers Squibb

PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Objectives

• Explain the underlying metabolic defects of type 2 diabetes and why so many patients fail to achieve treatment goals with the current treatment regimen.

• Identify the contribution of postprandial glucose concentrations to overall glycemic control.

• Review the pharmacological approaches to type 2 diabetes and their therapeutic mechanisms of action to include alternatives provided by the new incretin-related anti-diabetes agents.
What is Diabetes?

• A metabolic syndrome characterized by abnormalities in the metabolism of
  – Carbohydrates
  – Fats
  – Proteins
• Characterized by chronic hyperglycemia
• Associated with complications
Diabetes Costs in US in 2007

Indirect costs:
$58 billion
Disability, work loss, Premature mortality

Direct costs:
$116 billion
$27 B diabetes care
$58 B DM-related complications
$31 B excess gen’l medical costs

Total $174 Billion
Prevalence of Diabetes Mellitus

• 23.6 million children and adults
  – 8.0% of the population have diabetes
  – 17.9 million are diagnosed
  – 5.7 million are UNdiagnosed!
  – 23.1% of people over age 60 years have diabetes

• 57 million people have PREDIABETES!
Diabetes vs. Prediabetes

- **FPG < 100**
  - Normal

- **FPG 100-125**
  - Pre-diabetes

- **FPG ≥ 126**
  - DM

- **2 hr PP PG < 140**
  - Normal

- **2 hr PP PG 140-199**
  - Pre-diabetes

- **2 hr PP PG ≥ 200**
  - DM

Impaired Fasting Glucose

Impaired Glucose Tolerance

Copyright PharmCon 2009
Cormorbidities and Complications

- **Overweight and obesity – people with DM**
  - 55% are obese; 85% are overweight
  - 80% have insulin resistance

- **Macrovascular complications**
  - DM is the seventh leading cause of death
  - Heart attack, stroke, peripheral vascular disease

- **Microvascular complications**
  - Retinopathy, nephropathy

- **Neuropathic complications**
  - Autonomic, sensorimotor
Glucose Homeostasis

- Gastrointestinal Tract
- Hepatic System
- Musculoskeletal and adipose tissue
- Endocrine Pancreatic System
- Central nervous system

Campbell K. JAPhA 2009;49(suppl 1):S10-S15
Copyright PharmCon 2009
Audience Response!

• Why do you think less than half of all Americans with diabetes achieve their therapeutic goal?
• Please type in your thoughts.
Pathophysiology of T2DM

• Chronic insulin resistance (IR)
  – T2DM and chronic IR are highly correlated
    • > 80% individuals with T2DM have IR
    • IR common in obese individuals not diagnosed with T2DM
  – IR is detected earlier than beta-cell dysfunction in the pathogenesis of T2DM
  – IR appears to cause beta-cell dysfunction due to beta-cell exhaustion
    • Increased secretory demand due to peripheral tissue resistance

Campbell K. JAPhA 2009;49(suppl 1):S10-S15
Pathophysiology of T2DM

- Insulin resistance vs. beta-cell dysfunction
- While IR is not the primary cause of T2DM, it remains an important treatment target
  - An independent risk factor for atherosclerosis and cardiovascular disease
  - If untreated, promotes hyperglycemia and a glucotoxic environment
- Consensus opinion is that beta-cell dysfunction is primarily responsible for T2DM

Campbell K. JAPhA 2009;49(suppl 1):S10-S15
Beta-cell Dysfunction

- Beta-cell dysfunction may be due to glucotoxicity
  - Continued hyperglycemia may worsen beta cell function
  - Continued beta-cell dysfunction worsens glucotoxicity
- Activates stress response processes
- Lipotoxicity (increased FFA) decreases insulin synthesis and increases metabolic stress
- Amyloid deposits in beta-cells seen

Campbell K. JAPhA 2009;49(suppl 1):S10-S15
Incretin Hormones (GLP-1)

• Impaired incretion hormone action has also been associated with beta-cell dysfunction
• Incretins may be responsible for up to 70% of meal-induced insulin secretion
• Patients with T2DM have reduced incretin effect (< 50% normal)
  – GIP action abolished in T2DM
  – GLP-1 function may be preserved in T2DM, or pharmacologically augmented to near-normal levels

Campbell K. JAPhA 2009;49(suppl 1):S10-S15
Incretin Hormones (GLP-1)

• Beneficial effects on beta-cell include:
  – Beta-cell proliferation and neogenesis
  – Upregulation of insulin biosynthesis
  – Inhibition of beta-cell apoptosis
  – Improving beta-cell competence

Campbell K. JAPhA 2009;49(suppl 1):S10-S15
Importance of Glycemic Control

• Diabetes Control and Complications Trial
• United Kingdom Prospective Diabetes Study
  – Shown that normalizing glycosylated hemoglobin (A1c) levels in PWD reduced diabetes-related CV morbidity and mortality as well as microvascular complications
• 1% reduction in A1c (from UKPDS)
  – 37% reduction in microvascular complications
  – 43% reduction in amputation or PVD mortality
  – 21% reduction in any endpoint or mortality r/t DM
  – 14% reduction in MI

Campbell K. JAPhA 2009;49(suppl 1):S3-S9
# Recommendations for Adults with DM

<table>
<thead>
<tr>
<th>Metabolic Variable</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>&lt; 7%</td>
</tr>
<tr>
<td>Preprandial PG</td>
<td>70-130 mg/dl</td>
</tr>
<tr>
<td>Peak postprandial PG</td>
<td>&lt; 180 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt; 130/80 mmHg</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>&lt; 100 mg/dl without overt CVD</td>
</tr>
<tr>
<td></td>
<td>&lt; 70 mg/dl with overt CHD</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 150 mg/dl</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>&gt; 40 mg/dl men</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 mg/dl women</td>
</tr>
</tbody>
</table>

*American Diabetes Association, 2009*
Other Consensus Guidelines

• International Diabetes Federation
  – A1c < 6.5 %
  – 2 hour post-prandial < 140 mg/dl

• American Association of Clinical Endocrinologists / American College of Endocrinology
  – A1c < 6.5 %

A1c vs. eAG

- ADA has introduced the “estimated Average Glucose” as an alternate way to explain diabetes control to patients.
- A1c < 7.3% = 70% PPG influence
- A1c between 7.3 and 9.2% = PPG/FPG influence is equal

http://professional.diabetes.org/GlucoseCalculator.aspx
Postprandial Hyperglycemia

• Patients with “controlled” diabetes commonly have a normal FPG and elevated PPG
  – A FPG of 90 mg/dl can be associated with a 2 hour PPG of 200 mg/dl

• Elevated PPG levels are often the earliest sign of T2DM and may appear years before elevated FPG levels are observed
Consequences of PPHG and PP Glycemic Variability

- Adverse metabolic consequences include:
  - Increased oxidative stress
  - Abnormal vascular reactivity
  - Glycation
  - Hypercoagulability
  - Increased endothelial inflammation

- All these processes may be due to overproduction of superoxide, a reactive free radical

Clinical Implications of PPHG

- Strong association between PPG and cardiovascular disease

Clinical Implications of PPHG

• Data from the NHANES III showed patients with a 2 hour postprandial of 194 mg/dl had a three fold increase in incidence of retinopathy despite normal fasting glucose levels (< 110 mg/dl).

• Similar findings in other populations

Diabetes Care 1998; 22(suppl 1):S5-S19
Tier 1: Well-validated core therapies

At Diagnosis

Lifestyle + Metformin

Lifestyle + Metformin + Insulin

Lifestyle + Metformin + Sulfonylurea

Lifestyle + Metformin + Intensive Insulin

Step 1

Step 2

Step 3

Tier 2: Less well validated therapies

Lifestyle + Metformin + Pioglitazone

Lifestyle + Metformin + GLP-1 Agonist

Lifestyle + Metformin + Basal Insulin

Lifestyle + Metformin + Pioglitazone + SU

ADA and European Assoc for the Study of Diabetes
Audience Response!

• Given these guidelines and what you know about diabetes medications, how do you decide which medication to start with?

• Please record your thoughts.
Metformin

- MOA – Improves the effectiveness of insulin in suppressing excess hepatic glucose production
- Metformin is effective as monotherapy and in combination with other antidiabetes medications
- Adverse effects include metallic taste, anorexia, nausea, abdominal pain and diarrhea
  - Very rarely, lactic acidosis
**Sulfonylureas**

- MOA – Stimulate the delayed, second phase of insulin secretion after meal ingestion; little effect on the first-phase insulin secretion
- Sulfonylureas are effective as monotherapy and in combination with other antidiabetes medications such as metformin
- Adverse effects include hypoglycemia and weight gain
Thiazolidinediones (TZDs)

- First available in the mid-1990’s (troglitazone)
- Currently available pioglitazone and rosiglitazone
- MOA – insulin sensitizing agents; reduce both fasting and PP glucose concentrations
- Adverse effects - weight gain, increased bone fractures
  - Increased ischemic heart disease with rosiglitazone?
Metformin, SU and TZD on PPG Control

- Metformin, thiazolidinediones and sulfonylureas reduce PPG largely from a “phase shift” in plasma glucose
  - They lower PPG because they provide an overall improvement in hyperglycemia and lower PPG through a leveling effect
Glinides

• Repaglinide and nateglinide (glinides) are short-acting nonsulfonylurea secretagogues that increase early-phase insulin release and decrease total insulin secretion by reducing the second-phase insulin response
  – Decreased risk of postprandial hypoglycemia

• Useful in patients with irregular meal schedules
Alpha-Glucosidase Inhibitors

• Acarbose, miglitol
• MOA – competitive inhibitors of the alpha glucosidases, thereby delaying glucose absorption
  – Decreases glucose peak and insulin response postprandially and moderately lowers FPG levels and A1c
• Adverse effects - gastrointestinal
STOP-NIDDM Trial

Chiasson. JAMA 2003;290:486-94.
Figure 1. The Incretin Effect: Augmentation of Insulin Secretion Beyond the Effect of Glucose Alone

OGTT and Matched IV Infusion

Glucose (mg/dL)

- Oral
- IV

Insulin (pmol/L)

- Oral
- IV

Gut Factors – Incretin Hormones (INtestinal seCRETion of INsulin)

• 2 primary gut peptides
  – Glucose-dependent insulinotrophic peptide (GIP)
  – Glucagon-like peptide-1 (GLP-1)

• Gastrointestinal hormones released during nutrient absorption
  – Increases pancreatic insulin secretion in a glucose-dependent manner
  – Suppressing inappropriately elevated glucagon levels
  – Promoting satiety and reducing food intake
  – Slowing the rate of gastric emptying
Figure 1: Role of Incretins in Glucose Homeostasis

INGESTION OF FOOD

GI TRACT

DPP-4 enzyme

Release of gut hormones — Incretins

Active GLP-1 and GIP

GLP-1 and GIP

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide; DPP-4 = dipeptidyl-peptidase-4; GI = gastrointestinal.

GLUATE ALPA cells

Blood glucose

GLucose-dependent

 ↑Insulin from beta cells (GLP-1 and GIP)

↑Glucose uptake by muscles

↓Glucose production by liver

GLucose-dependent

↓Glucagon from alpha cells (GLP-1)

GLucose-dependent
GLP-1 Release Is Reduced in Type 2 Diabetes

*P<0.05 between type 2 diabetes and NGT groups.

Incretin-Based Therapies

- GLP-1 receptor agonist – exenatide
  - Resistant to DPP-4 degradation due to change in chemical structure
  - Given twice daily by SQ injection, for patients with T2DM not controlled on one or more oral agents
  - A1c reduction ranges from 0.4 to 0.9%
  - Reduces weight 0.9 to 3.1 kg; reduced BP
  - Shows marked reduction in PPG in clinical trials
  - Cases of pancreatitis reported
Metabolism of GIP and GLP-1

- Undergoes rapid and complete metabolism by the enzyme:
  - Dipeptidyl peptidase 4
  - DPP-4
- Half-life of GIP is 5-7 minutes
- Half-life of GLP-1 is about 2 minutes
Incretin-Based Therapies

- DPP-4 inhibitors
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Vildagliptin (awaiting approval; Galvus)

- Advantages include:
  - Good safety profile, low risk hypoglycemia
  - Reduce A1c by 0.8% or greater
  - Approved as first line agents
  - Preliminary data suggests agents may lower BP, and improve triglyceride level
<table>
<thead>
<tr>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robust glucose-lowering efficacy</td>
<td>Moderate glucose-lowering efficacy</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>Weight neutrality</td>
</tr>
<tr>
<td>Improvement in indices of beta-cell function</td>
<td>Improvement in indices of beta-cell function</td>
</tr>
<tr>
<td>Improvement in CV parameters (blood pressure, lipids, CV biomarkers)</td>
<td>No marked effects on CV parameters</td>
</tr>
<tr>
<td>Transient GI adverse effects</td>
<td>Little potential for GI adverse effects; increased headache, infection, dermatologic effects</td>
</tr>
</tbody>
</table>

Abbreviations used: CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1.
Other Therapies

- **Pramlintide**
  - Synthetic analogue of amylin, a beta-cell hormone
  - Injected preprandially, lowers plasma glucagon, delays gastric emptying, and promotes satiety
  - Reduces post-prandial hyperglycemia and facilitates weight loss
  - Used by patients with T2DM who use before-meal insulin
Other Therapies

• Insulin
  – Rapid-acting insulin analogues
    • Lispro (Humalog), aspart (NovoLog), glulisine (Apidra)
  – Premixed insulins
    • Lispro and insulin aspart with protamine (NovoLog Mix and Humalog Mix)
  – Basal long-acting insulin analogues
    • Glargine (Lantus) and Detemir (Levemir)
  – Less recommended: regular insulin and NPH
Conclusions

• Diabetes, particularly T2DM in growing alarmingly in prevalence.
• Glucose homeostasis is complicated, involving many pathways and messenger systems.
• The pathogenesis of T2DM includes IR, but beta-cell dysfunction is the primary culprit.
• Tighter blood glucose control leads to enhanced therapeutic outcomes.
Conclusions (continued)

- Postprandial hyperglycemia likely precedes the earliest sign of T2DM, occurring years before elevated FPG.
- Postprandial hyperglycemia is associated with cardiovascular disease and microvascular complications associated with diabetes.
Conclusions (continued)

• Diabetes medications that likely have a better effect on postprandial hyperglycemia include the alpha-glucosidase inhibitors, the glinides, and the incretin hormones.

• More evidence is required to evaluate the impact of the incretin hormones on postprandial hyperglycemia induced morbidity and mortality.
Managing Postprandial Glucose

What questions do you have?