Managing Postprandial Glucose

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

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

Total $174 Billion

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

Direct costs:
- $116 billion
  - $27 billion diabetes care
  - $58 billion DM-related complications
  - $31 billion excess general medical costs

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

Impaired Fasting Glucose
- FPG ≥ 126 → DM → Pre-diabetes
- FPG 100-125
- FPG < 100

Impaired Glucose Tolerance
- 2 hr PP PG ≥ 200
- 2 hr PP PG 140-199
- 2 hr PP PG < 140


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

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

Audience Response!

- Why do you think less than half of all Americans with diabetes achieve their therapeutic goal?
- Please type your thoughts in the chat box.
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

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

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

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
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</td>
</tr>
<tr>
<td>- without overt CVD</td>
<td>&lt; 70 mg/dl</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

ADA Consensus Guidelines

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

Copyright PharmCon 2009
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
Managing Postprandial Glucose

Audience Response!

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

---

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

---

Tier 1: Well-validated core therapies

- At Diagnosis
  - Lifestyle + Metformin
  - Lifestyle + Metformin + Insulin
  - Lifestyle + Metformin + Sulfonylurea

Step 1

Tier 2: Less well validated therapies

- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + GLP-1 Agonist

---

ADA and European Assoc for the Study of Diabetes
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
Gut Factors – Incretin Hormones (Intestinal seCREtion of Insulin)

- 2 primary gut peptides
  - Glucose-dependent insulinotropic 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

GLP-1 Release Is Reduced in Type 2 Diabetes

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

[Graph showing GLP-1 release during and after meals for NGT, IGT, and Type 2 Diabetes 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
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
    • Liargine (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.