Current Strategies for Post-prandial Glucose Control

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Reviewer
Michael Gabay, PharmD, JD, BCPS declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program.
Objectives

• Describe the pathophysiology of diabetes.
• Describe the use of both fasting and post-prandial glucose levels to assess glucose control.
• Explain the risks of uncontrolled post-prandial hyperglycemia.
• Identify medications that can be used to decrease post-prandial glucose levels per the ADA guidelines.
• Discuss basic characteristics of currently available post-prandial medications including mechanism of action, administration, common adverse effects, advantages, and disadvantages.
• Design an evidence-based medication regimen for a patient with post-prandial hyperglycemia.

The Scope of Diabetes

• In 2014, 29.1 million American adults had diabetes
• 90-95% have type 2 diabetes
• 5% have type 1 diabetes
• Increases risk of heart disease, stroke, retinopathy, kidney failure, amputation
• All patients with type 1 diabetes need insulin, but treatment of type 2 diabetes varies

The Scope of Diabetes Among US Adults (%)

![Treatment of Diabetes Among US Adults (%)]

- No Medication
- Oral Agents Only
- Orals + Insulin
- Insulin Only


Trends in Glycemic Control: NHANES 2010

![Trends in Glycemic Control: NHANES 2010]

A1C < 7%


Clinical Inertia in Type 2 Diabetes

• Retrospective cohort study of 81,573 people with type 2 diabetes
• Median time to intensification with insulin was > 6 years for patients on 2 or 3 OADs with A1C ≥ 7.5%
  - 2 OADs with A1C ≥ 7.5% = 7.2 years
  - 2 OADs with A1C ≥ 8% = 6.9 years
  - 3 OADs with A1C ≥ 7.5% = 6.1 years
  - 3 OADs with A1C ≥ 8% = 6.0 years

Treatment Options – T2DM

• Medications – Approved before 2000
  • Exogenous insulin (human and analogs)
  • Sulfonylureas
  • Biguanides (metformin)
  • Alpha-glucosidase inhibitors (AGIs)
  • Meglitinides
  • Thiazolidinediones (TZDs)

• Medications – Approved since 2005!
  • Amylin analogues (pramlintide)
  • Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)
  • Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)
  • Bile acid sequestrant (colesevelam)
  • Dopamine agonist (bromocriptine)
  • Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)

Pathophysiology of Type 2 Diabetes

HYPERGLYCEMIA

↓ Insulin Secretion
  • sulfonylureas

↑ Hepatic Glucose Output
  • metformin

↑ Insulin Resistance
  • thiazolidinediones

Natural History of T2D: β-cell function

Pancreatic function = 50% of normal

First Phase Insulin Response

Post-prandial Glucose in T2D
- Glucose levels after eating
- Depend on a variety of factors
  - Carbohydrate absorption
  - Insulin and glucagon secretion
  - Glucose metabolism
  - Timing, quantity, and composition of meal
- Often overlooked in the management of T2D
- Strong association between elevated PPG and cardiovascular outcomes, cardiovascular mortality, and microvascular complications
- PPG may be a better predictor of poor diabetes-related outcomes than FPG

Relative Contribution to Hyperglycemia

Pathophysiology of T2D

**Goals for Glycemic Control**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>A1C</th>
<th>FPG (mg/dL)</th>
<th>PPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>&lt; 7%</td>
<td>80-130</td>
<td>&lt; 180 1-2 hrs after meal</td>
</tr>
<tr>
<td>AACE</td>
<td>&lt; 6.5%</td>
<td>&lt; 110</td>
<td>&lt; 140 2 hrs after meal</td>
</tr>
</tbody>
</table>


**Pathophysiologic Approach to Treating T2D**


**ADA Management of Hyperglycemia in Type 2 Diabetes**

**Targeting Post-prandial Glucose in T2D**

- American Diabetes Association (ADA)
  - Treatment approach based on patient and treatment-specific factors
  - PPG testing recommended for patients who have pre-meal glucose values within target but have A1C values above target
  - If basal insulin has been titrated to acceptable fasting glucose levels, consider advancing to combination therapy to cover PPG

- American Association of Clinical Endocrinologists (AACE)
  - Treatment based on metabolic effects of treatments and patient-specific factors
  - PPG testing recommended in addition to FPG; no distinction or prioritization made

**Dietary Considerations**

- **Quantity** and type of carbohydrate influences PPG.
- Replace refined carbs and added sugars with whole grains, legumes, vegetables, and fruits.
- Avoid sugar-sweetened and low-fat or non-fat products with high amounts of added sugars.
- Intensive insulin regimens: match insulin administration with carb intake.

---

**Targeting the Glucose Profile**

<table>
<thead>
<tr>
<th>Targets Fasting Glucose</th>
<th>Metformin</th>
<th>Basal insulin</th>
<th>TZDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targets Post-Prandial Glucose</td>
<td>Meglitinides</td>
<td>Alpha-glucosidase inhibitors</td>
<td>GLP-1 agonists (short acting)</td>
</tr>
<tr>
<td>Targets both</td>
<td>Sulfonylureas</td>
<td>SGLT-2 inhibitors</td>
<td>GLP-1 agonists (long acting)</td>
</tr>
</tbody>
</table>

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**Meglitinides**

- Repaglinide (Prandin®), nateglinide (Starlix®)
- Increase insulin secretion
- Faster onset and shorter duration than SUs
- **Advantages**
  - Dosing flexibility
- **Disadvantages**
  - Hypoglycemia
  - Weight gain
  - Frequent dosing schedule
- **Cost** – Moderate

---

**Alpha-glucosidase inhibitors (AGIs)**

- Acarbose (Precose®), miglitol (Glyset®)
- Slows intestinal carbohydrate ingestion/absorption
- **Advantages**
  - Low hypoglycemia risk
  - Non-systemic
  - No weight gain
- **Disadvantages**
  - Modest A1C effect
  - GI side effects
  - Frequent dosing schedule
- **Cost** – Moderate
GLP-1 RAs: Actions on Target Tissues

- **Pancreas**: ↑Glucose-dependent insulin secretion, ↓Glucose-dependent glucagon secretion
- **Stomach**: ↓Gastric emptying
- **Brain**: ↑Satiety

GLP-1 RAs: Comparisons

<table>
<thead>
<tr>
<th>GLP-1 RAs: Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta®, Bydureon®), liraglutide (Victoza®), albiglutide (Tanzeum®), dulaglutide (Trulicity®)</td>
</tr>
<tr>
<td>Increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, slows gastric emptying, increases satiety</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>- Low hypoglycemia risk</td>
</tr>
<tr>
<td>- Reduces weight</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>- GI side effects</td>
</tr>
<tr>
<td>- Injectable</td>
</tr>
<tr>
<td><strong>Cost – High</strong></td>
</tr>
</tbody>
</table>


ADA Management of Hyperglycemia in Type 2 Diabetes

GLP-1 RAs: Comparisons

<table>
<thead>
<tr>
<th>Generic (Brand) Name</th>
<th>Short-Acting GLP-1 RAs</th>
<th>Long-Acting GLP-1 RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide (Byetta)</td>
<td>Liraglutide (Victoza)</td>
</tr>
<tr>
<td></td>
<td>Listexenatide (Epeumis)</td>
<td></td>
</tr>
<tr>
<td>FDA approval</td>
<td>2005</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>Pending</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014</td>
</tr>
<tr>
<td>Glucose profile</td>
<td>PPG</td>
<td>PPG/PPG</td>
</tr>
<tr>
<td></td>
<td>FPG/PPG</td>
<td>FPG/PPG</td>
</tr>
<tr>
<td></td>
<td>FPG/PPG</td>
<td>FPG/PPG</td>
</tr>
<tr>
<td></td>
<td>FPG/PPG</td>
<td>FPG/PPG</td>
</tr>
<tr>
<td>Dose</td>
<td>5-10 mcg</td>
<td>10-20 mcg</td>
</tr>
<tr>
<td></td>
<td>0.6-1.8 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td></td>
<td>30-50 mg</td>
<td>0.75-1.5 mg</td>
</tr>
<tr>
<td>Admin</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td></td>
<td>Once daily</td>
<td>Once weekly</td>
</tr>
<tr>
<td></td>
<td>Once weekly</td>
<td>Once weekly</td>
</tr>
<tr>
<td></td>
<td>Once weekly</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Delivery</td>
<td>Multi-use pen</td>
<td>Multi-use pen</td>
</tr>
<tr>
<td></td>
<td>Multi-use pen*</td>
<td>Single-use pen</td>
</tr>
<tr>
<td></td>
<td>Single-use pen*</td>
<td>Single-use pen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single-use pen</td>
</tr>
<tr>
<td>Renal dosing</td>
<td>&lt;30 not rec; 30-50 use caution</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30 not rec; 30-50 use caution</td>
</tr>
</tbody>
</table>

*Requires reconstitution
## Comparison of Phase 3 Studies

<table>
<thead>
<tr>
<th>Phase 3 Clinical Trials</th>
<th>Exenatide (Byetta®)</th>
<th>Lixisenatide (Lyxumia®)</th>
<th>Liraglutide (Victoza®)</th>
<th>Exenatide XR (Bydureon®)</th>
<th>Albiglutide (Tanzeum®)</th>
<th>Dulaglutide (Trulicity®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Back-ground Therapy</strong></td>
<td>Drug naïve, metformin, SU</td>
<td>Drug naïve, metformin, SU, TZD</td>
<td>Drug naïve, metformin, SU, TZD</td>
<td>Drug naïve, metformin, SU, TZD</td>
<td>Drug naïve, metformin, SU, TZD, basal insulin</td>
<td>Drug naïve, metformin, SU, TZD, basal insulin</td>
</tr>
<tr>
<td><strong>A1C lowering (%)</strong></td>
<td>0.4 to -1.36</td>
<td>0.7 to -1.0</td>
<td>0.6 to -1.48</td>
<td>1.3 to -1.9</td>
<td>-0.55 to -0.90</td>
<td>-0.42 to -1.51</td>
</tr>
<tr>
<td><strong>Weight lowering (kg)</strong></td>
<td>-0.9 to -3.1</td>
<td>-0.2 to -2.96</td>
<td>-0.6 to -4.7</td>
<td>-2.0 to -1.7</td>
<td>+0.28 to -1.21</td>
<td>-0.2 to -3.03</td>
</tr>
</tbody>
</table>

*Includes all doses studied.

## GLP-1 RAs + Basal Insulin

### GLP-1 Agonists
- Fasting and postprandial glycemic control
- Weight reduction
- Low hypoglycemic risk
- GI adverse effects

### Basal Insulin
- Fasting glycemic control
- Individualized dosing
- Hypoglycemic risk
- Weight gain

## GLP-1 RAs + Basal Insulin

- **Meta-analysis:** 15 studies included
- **GLP-1 RA + basal insulin vs. other treatments**
- **Variety of background therapies and active comparators**
- **Results**
  - Improved mean reduction in A1C of -0.44% (95% CI, -0.60 to -0.29)
  - No increased relative risk of hypoglycemia (HR 0.99; 95% CI, 0.76–1.29)
  - Mean reduction in weight of -3.22 kg (95% CI, -4.90 to -1.54)

### GLP-1 RAs vs. Bolus Insulin

<table>
<thead>
<tr>
<th>Clinical Trial (Duration)</th>
<th>Background Therapy</th>
<th>Comparator Arms</th>
<th>Change in A1C (%)</th>
<th>Change in weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamant (30 weeks)</td>
<td>Glargine + metformin</td>
<td>Exenatide</td>
<td>-1.13*</td>
<td>-2.5*</td>
</tr>
<tr>
<td>Rosenstock (26 weeks)</td>
<td>Glargine + metformin, pioglitazone, or both</td>
<td>Lispro with each meal</td>
<td>-1.10</td>
<td>+2.1</td>
</tr>
<tr>
<td>Mathieu (28 weeks)</td>
<td>Degludec + metformin</td>
<td>Liraglutide</td>
<td>-0.74*</td>
<td>-2.8*</td>
</tr>
<tr>
<td>Roy-Duval (26 weeks)</td>
<td>Glargine + metformin</td>
<td>Lusinamide</td>
<td>-1.34*</td>
<td>-0.7*</td>
</tr>
</tbody>
</table>

*Met noninferiority criteria. *p<0.05.

GLP-1 RAs vs. Bolus Insulin

- Better patient satisfaction
- More GI adverse effects
- Less hypoglycemia


DPP4 inhibitors: Actions on Target Tissues

- Pancreas: ↑Glucose-dependent insulin secretion, ↓Glucose-dependent glucagon secretion
- Stomach: ↓Gastric emptying
- Brain: ↑Satiety

DPP-4 Inhibitors

- Sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), alogliptin (Nesina®)
- Increase insulin secretion, decrease glucagon secretion
- Advantages
  - Low hypoglycemia risk
  - No weight gain
  - Well tolerated
- Disadvantages
  - Modest A1C effect
  - Concern for heart failure hospitalizations with saxagliptin, alogliptin
- Cost – High

### DPP-4 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose/ frequency</strong></td>
<td>100 mg once daily</td>
<td>5 mg once daily</td>
<td>5 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td><strong>Efficacy (A1C lowering): monotherapy</strong></td>
<td>▼ 0.6%</td>
<td>▼ 0.7%</td>
<td>▼ 0.4%</td>
<td>▼ 0.8%</td>
</tr>
<tr>
<td><strong>Efficacy (A1C lowering): combination therapy</strong></td>
<td>▼ 0.7%</td>
<td>▼ 1.2%</td>
<td>▼ 0.7%</td>
<td>▼ 0.9%</td>
</tr>
<tr>
<td><strong>Renal dosing</strong></td>
<td>50 mg daily (moderate)</td>
<td>25 mg daily (severe)</td>
<td><strong>No dose adjustment necessary</strong></td>
<td>12.5 mg daily (moderate)</td>
</tr>
</tbody>
</table>

Baetta R. Drugs 2011;71:1441-1467.

### DPP-4 Inhibitors vs. GLP-1 RAs: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>DPP-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodyl</td>
<td>▼ 0.6</td>
<td>▼ 0.9</td>
</tr>
<tr>
<td>Clerexan</td>
<td>▼ 0.7</td>
<td>▼ 1.2</td>
</tr>
<tr>
<td>Bergenstal (DURATION 2)</td>
<td>▼ 0.9</td>
<td>▼ 1.1</td>
</tr>
<tr>
<td>Russell-Jones (DURATION 4)</td>
<td>▼ 0.6</td>
<td>▼ 0.8</td>
</tr>
<tr>
<td>Mone (HARMONY 3)</td>
<td>▼ 0.3</td>
<td>▼ 0.5</td>
</tr>
<tr>
<td>Istar (HARMONY 8)</td>
<td>▼ 0.6</td>
<td>▼ 0.8</td>
</tr>
<tr>
<td>Sauck (AWARD 5)</td>
<td>▼ 0.3</td>
<td>▼ 0.9</td>
</tr>
</tbody>
</table>


### ADA Management of Hyperglycemia in Type 2 Diabetes


### Renal Glucose Handling

SGLT-2 Inhibitors

- Canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance)
- Inhibit glucose reabsorption
- Lower renal glucose threshold
- Increase urinary glucose excretion
- Do not specifically target FPG or PPG; lower glucose indiscriminately when elevated
- Glucose loss – 80–100 g/day – 320–400 kcal/day
- Lower weight, lowers BP
- Low risk of hypoglycemia
- Most common AE – genitourinary infections

Approximate PK Profiles of Insulin Types

PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Insulin

Meal-time insulin
- Human regular insulin (Humulin R®, Novolin R®)
- Rapid-acting insulin analog (insulin aspart [Novolog®], insulin lispro [Humalog®], insulin glulisine [Apidra®])
- Biphasic pre-mixed insulin (several types)
- Inhaled insulin (Afreza®)

Advantages
- Nearly universal response
- Theoretically unlimited efficacy

Disadvantages
- Hypoglycemia
- Weight gain
- Injectable (except for inhaled)
- Training requirements

Insulin therapy in T1D

- Intensive insulin (MDI or insulin pump)
- ~ 50% basal + 50% bolus (prandial)
- Goal of prandial insulin therapy is to reduce PPG by trying to mimic the endogenous insulin secretion pattern
  - Minimize the quick rise in glucose
  - Avoid late postprandial hypoglycemia
- Dosing is patient specific
- Matching the dose of prandial insulin to estimated carb intake should be considered

Aspart
Pract
41
ADA and AACE recommend RAIAs over regular
S, et al. 2010 meta
Technol.
less 2016;22(1):84
98
35
85
264
43
94
31
184
Insulin
Regular Human
Insulin
Glulisine
Management of Hyperglycemia in Type 2 Diabetes
Injections
Onset
(min)
Peak
(min)
Duration
(min)
Insulin Aspart
41
94-104
264
Insulin Lispro
35-46
85-198
184-313
Insulin Glulisine
31-34
98-196
218-238
Regular Human
Insulin
43-61
156-193
306-415
After a mixed meal, endogenous
insulin has an onset of 16-18
minutes and peaks within 30-45
minutes.

Rapid-Acting Insulin Analogs vs.
Regular Insulin

• 2010 meta-analysis of 50 studies in T1D and
30 studies in T2D
  – RAIAs better than regular insulin at reducing A1C
  and nocturnal hypoglycemia in T1D
  – Benefits not as pronounced or consistent in T2D
• ADA and AACE recommend RAIAs over regular insulin
  – Better PPG control and less hypoglycemia


ADA Management of Hyperglycemia in Type 2 Diabetes

ADA: Starting and Adjusting Insulin in T2D

RAIAn: rapid-acting insulin analog
Canadian Agency for Drugs and Technologies in Health. CANDTH Technical Overview 2016.11(e).0110.


Patient Education: Insulin

- Administration and timing
- Injection technique and site rotation
- Storage and disposal
- Dosing
- Self-monitoring of blood glucose (SMBG)
  - Using a glucometer, timing, expected goals, interpreting & using data
- Hypoglycemia: prevention, detection, treatment

Meta-Analysis: Weight Changes with Antihyperglycemic Agents Added to Metformin

![Graph showing weight changes with different antihyperglycemic agents vs placebo.]

Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

![Graph showing increased and decreased risk of hypoglycemia with different agents.]

Patient Case

HPI:
Mr. Jenkins is a 60-year-old Caucasian male who was diagnosed with T2D 10 years ago. He is currently being treated with metformin 1000mg twice daily and insulin glargine 62 units once daily. In the past he has tried glyburide which was discontinued due to hypoglycemia and pioglitazone which was discontinued due to edema. He is adherent to his medications and is tolerating them without side effects.
Patient Case

Past Medical History:
- Type 2 Diabetes x 10 years
- Dyslipidemia x 12 years
- Hypertension x 12 years
- Depression x 5 years

Home Medications:
- HCTZ 12.5mg once daily
- Insulin glargine 62 units daily
- Losartan 100mg once daily
- Metformin 1000mg twice daily
- Rosuvastatin 10mg once daily
- Sertraline 100mg once daily

Social and Family History:
- Divorced, lives alone
- Previous smoker
- Works full time at the airport
- 2 siblings and mother with diabetes
- Eats out often; does not enjoy cooking; eats pre-made meals at home
- Walks at work; no other exercise

Laboratory Data:
- Glucose = 203 mg/dL
- A1C = 8.4%
- Na = 142 mg/dL
- K = 4.7 mg/dL
- Scr = 1.2 mg/dL
- eGFR = 66 mL/min
- Total chol = 170 mg/dL
- LDL = 83 mg/dL
- HDL = 44 mg/dL
- TG = 172 mg/dL

Vital Signs:
- BP = 136/84
- HR = 76 bpm, regular
- Height = 5’11”
- Weight = 254 lb
- BMI = 35.4 kg/m²

Glucometer Data: (30 days)
- FPG = 139 mg/dL (88-151)
- PPG = 246 mg/dL (188-320)

• Considerations
  - Glucose Profile and A1C
  - Non-drug therapy changes
  - Basal insulin dose
  - Past diabetes medications
  - Contraindications/adverse effects
  - Cost, ease of use, patient collaboration

Questions
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