Achieving Glycemic Control: When Optimized Basal Insulin Isn’t Adequate

AAFP State Chapter Meeting

Faculty Louis Kuritzky MD
Clinical Assistant Professor Emeritus
Department of Community Health and Family Medicine
College of Medicine
University of Florida, Gainesville
Statements of Sponsorship and Support

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Primary Care Education Consortium

Primary Care Metabolic Group

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Register at: www.pcmg-us.org
Learning Objectives

After completing this program, the primary care provider should be able to:

• Identify patients who have reached the likely maximum benefits of their optimized basal insulin

• Compare medications available for use in combination with basal insulin to lower postprandial glucose

• Compare the outcomes of patients treated with the addition of prandial insulin vs a GLP-1RA to basal insulin
CME Information

This Live activity, Achieving Glycemic Control: When Optimized Basal Insulin Isn’t Adequate, from 04/15/2015 - 04/15/2016, has been reviewed and is acceptable for up to 1.00 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Faculty Disclosure

Louis Kuritzky, MD discloses that he is on the advisory board for Amgen, Boehringer Ingelheim, Daiichi Sankyo, Janssen, Lilly, Novo Nordisk, Sanofi, and Takeda Pharmaceuticals.

He is on the speakers’ bureau for Amgen, Lilly, and Novo Nordisk.
Case Study- Alison

- 48 yo female diagnosed with T2DM 8½y ago
  - 10 months ago
    - HbA1c 8.6%, FPG 138-164 mg/dL despite metformin + SU
    - Basal insulin added, SU discontinued

- Basal insulin titrated; now 58 units (0.56 units/kg) at dinner
  - HbA1c 7.6%
  - Glucose: fasting 92-133 mg/dL; bedtime 162-190 mg/dL

- 2 episodes of symptomatic hypoglycemia during past 3 mos; last episode causing a fall

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>Insulin initiated</th>
<th>Now</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>97.3</td>
<td>99.1</td>
<td>102.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.5</td>
<td>34</td>
<td>35.4</td>
</tr>
</tbody>
</table>
Patients with Diabetes Have Basal and Prandial Hyperglycemia

Adapted from: Riddle M. Pract Cardiol. 1986;12:65-79.
Desirable Clinical Effects of Basal Insulin

- **Basal analog insulin**
  - Long-acting (24 hours)
  - Peakless (doses <0.5 units/kg)
  - Reduces hepatic glucose production (gluconeogenesis, glycogenolysis) and lipogenesis
  - Primarily targets fasting plasma glucose
  - Approximately 60% of patients with T2DM can achieve HbA$_{1c}$ ≤ 7.0% with basal insulin (+ oral agents) if taken CONSISTENTLY

What is Meant by Optimized Basal Insulin?

**Efficacy**
- HbA$_1c$ at goal
- ≤7% for this patient
- FPG 80-130 mg/dL

**Safety/Tolerability**
- Minimize hypoglycemia
- Severe
- Nocturnal
- Minimize weight gain

**Patient Factors**
- Needs, interests, capabilities
  - Schedule/Lifestyle
  - Occupation
  - SMBG

When Basal Insulin May Not Be Enough to Achieve Glycemic Control

- **HbA$_{1c}$ >7.0%, despite FPG 80-130 mg/dL**

- **And…**
  - Total basal insulin dose exceeds 0.5-1 unit/kg/day$^1$
  - Severe, nocturnal, or frequent symptomatic hypoglycemia
  - Difference between bedtime and AM (BeAM) blood glucose >55 mg/dL$^2$
    - Less likely to achieve HbA$_{1c}$ ≤7.0%
    - Increased risk of nocturnal hypoglycemia
  - Weight gain

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Increasing doses of basal insulin may lead to diminishing returns

Moreover,
- Reduction in the HbA1c plateaus
- Incidence of hypoglycemia (blood glucose ≤56 mg/dL) rises over time

Avoiding Overbasalization

• If the basal insulin dose is correct, the bedtime BG should be about the same as the next morning’s FPG (assuming no prandial insulin at nighttime)

• If the BG decreases significantly overnight (ie, BeAM>55 mg/dL), the basal dose is too high

• If the BG increases significantly overnight, the basal dose is too low
  • Caution to avoid Dawn Phenomenon

BeAM, bedtime to pre-breakfast
# Glycemic Effects of Glucose-Lowering Medications

<table>
<thead>
<tr>
<th>Glycemic Effects</th>
<th>Fasting Plasma Glucose Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutral</td>
</tr>
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</tr>
<tr>
<td>Mild</td>
<td>• Bromocriptine</td>
</tr>
<tr>
<td>Moderate</td>
<td>• AGi</td>
</tr>
<tr>
<td>Moderate/Marked</td>
<td>• Rapid-/Short-acting Insulin</td>
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</table>

<sup>a</sup>FPG lowering: mild- albiglutide, exenatide BID; moderate- dulaglutide, exenatide QW, liraglutide

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As a patient’s HbA$_{1c}$ approaches 7%, controlling the postprandial glucose ___ the fasting plasma glucose.

1. Becomes more important than
2. Becomes less important than
3. Remains as important as
Fasting vs Postprandial Glucose Contribution to HbA$_{1c}$

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Importance of Postprandial Glucose

Increasing 2-hour PPG is associated with an increasing risk of all-cause mortality, particularly for PPG ≥200 mg/dL

Importance of Postprandial Glucose (cont)

Hyperglycemic spikes following every meal induce oxidative stress, endothelial dysfunction, and inflammatory reactions.
Case Study- Alison

- 48 yo female diagnosed with T2DM 8½ y ago
- Current Treatment
  - Metformin + basal insulin 58 units at dinner
- Glucose levels
  - HbA$_{1c}$ 7.6%
  - Fasting 92-133 mg/dL
  - Bedtime 162-190 mg/dL
- 2 episodes of symptomatic hypoglycemia during past 3 mos; last episode causing a fall

How should her treatment be modified?
Healthy eating, weight control, increased physical activity & diabetes education

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (or any specific preference – choice dependent on a variety of patient- & disease-specific factors):

- Metformin + Sulfonylurea
- Metformin + Thiazolidinedione
- Metformin + DPP-4 inhibitor

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (or any specific preference – choice dependent on a variety of patient- & disease-specific factors):

- Metformin + Sulfonylurea + TZD
- Metformin + Thiazolidinedione + DPP-4 inhibitor
- Metformin + GLP-1-RA + Insulin

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

- Metformin + Insulin (basal)
- Metformin + DPP-4-i
- Metformin + GLP-1-RA

This is Alison’s current treatment

These are the options for intensifying basal insulin

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*FPG lowering: mild- albiglutide, exenatide BID; moderate- dulaglutide, exenatide QW, liraglutide

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Other Considerations in Selecting Therapy to Lower Postprandial Glucose

- **Medication Factors**
  - Magnitude/Durability of response
  - Mechanism of action
  - Requirement for functioning β-cell
  - Adverse events
  - Warnings/Contraindications
  - Cost/Insurance

- **Patient Factors**
  - Body weight
  - Regularity/Quality of meals
  - Variations in physical activity/work schedule
  - Hypoglycemia awareness/tolerance
  - Adherence
Pathophysiologic Mechanisms in Hyperglycemia of T2DM

- Liver: ↑ Hepatic glucose secretion
- Pancreas: ↓ Insulin secretion, ↑ Glucagon secretion
- Gut: Diminished incretin effect, Altered intestinal glucose absorption
- CNS: Delayed satiety
- Kidney: ↑ Glucose reabsorption
- Muscle and adipose tissue: ↓ Glucose uptake
Healthy eating, weight control, increased physical activity & diabetes education

<table>
<thead>
<tr>
<th>Metformin</th>
<th>High</th>
<th>Low risk</th>
<th>Neutral/loss</th>
<th>GI / lactic acidosis</th>
<th>Low</th>
</tr>
</thead>
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If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

- **Metformin +**
  - Sulfonylurea
  - Thiazolidinedione
  - DPP-4 inhibitor
  - SGLT2 inhibitor
  - GLP-1 receptor agonist
  - Insulin (basal)

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

- **Metformin +**
  - Sulfonylurea +
    -TZD
    - DPP-4-i
    - SGLT2-i
    - GLP-1-RA
    - Insulin
  - Thiazolidinedione +
    - SU
    - DPP-4-i
    - SGLT2-i
    - GLP-1-RA
    - Insulin
  - DPP-4 inhibitor +
    - SU
    - TZD
    - DPP-4-i
    - GLP-1-RA
  - SGLT2 inhibitor +
    - SU
    - TZD
    - DPP-4-i
  - GLP-1 receptor agonist +
    - SU
    - TZD
  - Insulin (basal)

In refractory patients consider adding TZD or SGLT2-i:

**Metformin +**

- Basal Insulin +
  - Mealtime Insulin or
  - GLP-1 RA

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Case Study- Alison

Metformin + Basal Insulin

Which should be added?

- Rapid-/Short-acting Insulin
- GLP-1 Receptor Agonist
- DPP-4 Inhibitor
- SGLT-2 Inhibitor

- HbA$_{1c}$ 7.6%
- FPG 92-133 mg/dL
- Bedtime 162-190 mg/dL
- Symptomatic hypoglycemia
- Weight gain
## Case Study - Alison (cont)

<table>
<thead>
<tr>
<th>Alison...</th>
<th>Rapid-/Short-acting Insulin</th>
<th>GLP-1 Receptor Agonist</th>
<th>DPP-4 Inhibitor</th>
<th>SGLT-2 Inhibitor</th>
</tr>
</thead>
</table>
| is concerned about: | • Further hypoglycemia  
• Further weight gain  
• Potential for multiple daily injections | • Additional injection  
• Transient N/V  
• ?Acute pancreatitis  
• C-cell hyperplasia/medul-lary thyroid tumors in animals | • Immune-mediated dermatologic effects  
• ?Acute pancreatitis  
• ?Heart failure hospitalizations | • Genital yeast infections  
• Polyuria  
• Volume depletion/hypo-tension/dizziness  
• ↑ LDL-C  
• ↑ Creatinine (transient) |
| likes: | • Potential for weight loss  
• Low risk of hypoglycemia  
• Potential for reducing basal insulin dose | • Potential for no further weight gain  
• Low risk of hypoglycemia  
• Oral | | • Potential for weight loss  
• Low risk of hypoglycemia  
• Oral |

Bolus Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin

- Adults with T2DM
- HbA$_{1c}$ 7.0-10.0%
- Receiving insulin glargine plus metformin

Glargine optimization over 12 wks to achieve FPG $\leq$100 mg/dL

Those who didn’t achieve HbA$_{1c}$ $\leq$7.0%...

Exenatide 10-20 mcg BID ($\downarrow$ Basal Insulin $\geq$10%)

30 weeks

Lispro TID ($\downarrow$ Basal Insulin 33-50%)

Bolus Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin (cont.)

-1.5
-1
-0.5
0

Weeks Following Randomization

Exenatide BID
Lispro TID

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Bolus Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin (cont.)

ΔFasting Glucose* (mg/dL)

*P=0.002 for all time points except 0

Blood Glucose (mg/dL)

#P<.001

Dotted line: At randomization
Solid line: Study end
Bolus Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin (cont.)

Change in Key Endpoints*

- *P<.001 for all key endpoints

Bolus Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin (cont.)

<table>
<thead>
<tr>
<th>Study Results: Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c reduction</td>
</tr>
<tr>
<td>FPG reduction</td>
</tr>
<tr>
<td>PPG reduction</td>
</tr>
<tr>
<td>Minor hypoglycemia</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
</tr>
<tr>
<td>Weight change</td>
</tr>
<tr>
<td>Glargine dose</td>
</tr>
<tr>
<td>Treatment satisfaction</td>
</tr>
</tbody>
</table>

Basal insulin in combination with a GLP-1R agonist does not lead to a:

1. Higher incidence of major hypoglycemia (<54 mg/dL) compared with basal insulin alone
2. 1-2 kg average weight loss compared with basal insulin alone
3. 0.5-0.7% average HbA$_{1c}$ reduction compared with either alone
Exenatide BID vs. Placebo Add-on Therapy to Insulin Glargine + Oral Agents

T2DM

- HbA\textsubscript{1c} 7.1-10.5%
- Receiving insulin glargine alone or in combination with metformin or pioglitazone or both

Exenatide 10 mcg BID

137

1:1

30 weeks

Placebo

122

Exenatide BID vs. Placebo as Add-on Therapy to Insulin Glargine + Oral Agents (cont.)

<table>
<thead>
<tr>
<th>% Achieving HbA$_{1c}$ &lt;7.0%</th>
<th>ΔBody Weight (kg)</th>
<th>ΔInsulin Dose (U/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-2</td>
<td>0.25</td>
</tr>
<tr>
<td>25</td>
<td>-1.5</td>
<td>0.20</td>
</tr>
<tr>
<td>50</td>
<td>-1</td>
<td>0.15</td>
</tr>
<tr>
<td>75</td>
<td>-0.5</td>
<td>0.10</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*P < .001

Exenatide BID vs. Placebo as Add-on Therapy to Insulin Glargine + Oral Agents (cont.)

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Exenatide BID vs. Placebo as Add-on Therapy to Insulin Glargine + Oral Agents (cont.)

There were no episodes of major hypoglycemia (blood glucose < 54 mg/dL resulting in loss of consciousness or seizure responding to glucose/glucagon, or requiring assistance)

Insulin Detemir as Add-on Therapy to Metformin + Liraglutide: Study Design

- Patients with T2DM treated with metformin (HbA$_{1C}$ 7-10%) or metformin + SU (HbA$_{1C}$ 7-8.5%)
- 12-wk run-in: SU DC’d; liraglutide initiated, titrated to 1.8 mg/d
- After run-in:
  - If HbA$_{1C}$ $\geq$ 7.0%:
    - Continued metformin + liraglutide OR
    - Added insulin detemir 10 units evening/bedtime and titrated to FPG 74-108 mg/dL
  - If HbA$_{1C}$ < 7.0%:
    - Continued metformin + liraglutide (observational group)

Insulin Detemir as Add-on Therapy to Metformin + Liraglutide\(^1\) (cont.)

**Change in HbA\(_{1c}\) (%)**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Liraglutide + Detemir</th>
<th>Liraglutide</th>
<th>Liraglutide (obs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Weeks 0-26

**SMBG (mg/dL)**

- Fasting
- BF 90 min Pp
- Pre-Lunch
- LU 90 min Pp
- Pre-Dinner
- DI 90 min Pp
- Bedtime

\(*P=\cdot0003\)

\(**P=\cdot0244\)

\(#P=\cdot0141\)

\(\text{Randomization}\)

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Insulin Detemir as Add-on Therapy to Metformin + Liraglutide\(^1\) (cont.)

Change in Body Weight (kg)

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide + Detemir</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>-0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Rate of Minor Hypoglycemia (events/participant-year)

- No major hypoglycemia occurred during weeks 0-26
- \(* P = .03\)
- \(** P = .004\)


\(^1\)Weeks 0-26; *P* = .03; **P* = .004
Efficacy Results from Observational Studies of Basal Insulin in Combination with a GLP-1RA

Conclusion: Combination therapy improved glycemic control without weight gain or an increased risk of hypoglycemia.

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## GLP-1 Receptor Agonists in Combination with Insulin

<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th>Approved for Use in Combination with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal Insulin</td>
</tr>
<tr>
<td>Albiglutide QW</td>
<td>✔</td>
</tr>
<tr>
<td>Dulaglutide QW</td>
<td></td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>✔</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td></td>
</tr>
<tr>
<td>Liraglutide QD</td>
<td>✔</td>
</tr>
</tbody>
</table>

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Summary

• Residual postprandial hyperglycemia may prevent achieving HbA$_1c$ target
• Postprandial hyperglycemia is associated with cardiovascular risk
• Basal insulin may not be enough to achieve glycemic control
• Rapid-/Short-acting insulin has been the standard to lower postprandial glucose; however, ... compared with thrice-daily rapid-acting insulin, a GLP-1RA provides
  • Similar or better glycemic control
  • Less nocturnal hypoglycemia
  • Weight loss (vs gain)
  • Greater treatment satisfaction
Achieving Glycemic Control:
When Optimized Basal Insulin Isn’t Adequate

AAFP State Chapter Meeting

Louis Kuritzky MD
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