Combatting T2DM Clinical Inertia: Evaluating the Evidence For Simultaneous Basal Insulin and GLP-1 Receptor Agonists

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Combatting T2DM Clinical Inertia: Evaluating the Evidence For Simultaneous Basal Insulin and GLP-1 Receptor Agonists
Learning Objectives

Upon completion, participants should be able to:

• Describe the consequences of long-standing inefficient glycemic control in T2DM
• Outline the benefits and limitations of insulin used in combination with a GLP-1 receptor agonist
• Integrate evidence-based, timely intensification strategies for T2DM

Diabetes and Prediabetes in the United States

• **Prevalence:** 30.3 million people, or 9.4% of the US population
  – Approximately 1.25 million children and adults have type 1 diabetes
• **Undiagnosed:** 7.2 million people
• **New cases:** 1.5 million every year
• **Prediabetes:** 84.1 million adults
• **Deaths:** seventh leading cause of death

Diabetes in the United States

West Virginia has the highest rate of diabetes at 15 percent. The 11 states with the highest type 2 diabetes rates are in the South. Nationwide, diabetes rates have nearly doubled in the past 20 years—from 5.5 percent (1994) to 9.3 percent in 2012. More than 29 million American adults have diabetes and another 86 million have prediabetes. The CDC projects that one in three adults could have diabetes by 2059. More than one-quarter of seniors (age 65 and older) have diabetes (19.5 percent, or 11 million seniors). Diabetes is the seventh leading cause of death in the United States, accounting for around $355 billion in medical costs and lost productivity each year. (Note: The reported diabetes rates are crude rates from 2011-2014 and age-adjusted rates for 2015 and 2016.)

Diabetes Rate by State, 2016

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<tr>
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<th>State</th>
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<th>95% Confidence Interval</th>
<th>Trend 1990-2016</th>
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<td>≈ 9.2% - 13.0%</td>
<td>Study not available</td>
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Age-Adjusted Prevalence of Diagnosed Diabetes Among US Adults: 2015

Meet Brittany

• 37-year-old African American mother of 4
• T2DM for the past 5 years
• Gestational diabetes with last 2 pregnancies:
  – Controlled with diet, exercise, and oral medications
  – Her blood sugars did not normalize following the birth of her last child 5 years ago
  – Initially started on metformin 1 g twice daily
  – 2 years ago: added glimepiride and titrated to 4 mg orally twice daily
  – 6 months ago: added sitagliptin 100 mg daily
  – Tried pioglitazone; stopped because of lower extremity edema
Meet Brittany (cont.)

• Past medical history:
  – Grade 2 obesity (BMI > 38 kg/m²)
  – Gestational diabetes with macrosomic delivery (last child was 10 lb 2 oz at delivery)
  – HTN
  – Hyperlipidemia
  – Acanthosis nigricans

• Past surgical history:
  – Cesarean delivery 5 years ago due to macrosomic infant
  – Appendectomy at 21 years old

Diabetes Medications:
• Metformin 1 g PO BID
• Glimepiride 4 mg PO BID
• Sitagliptin 100 mg PO QD

A Little Background on Brittany

• Family history:
  – T2DM: mother, maternal grandmother, and maternal aunts
  – Renal failure: aunt with diabetes
  – PVD: maternal grandmother required amputation due to diabetic foot ulcer

• Social history:
  – Works at insurance company call center (desk job)
  – Picks up kids after work; husband works second shift
  – Meals are typically fast food/vending machine
  – Minimal exercise on weekends
  – Nonsmoker, rarely uses alcohol (never to excess), no drugs
A Little Background on Brittany (cont.)

- **Medications:**
  - Losartan 50 mg orally daily
  - HCTZ 25 mg orally daily
  - Simvastatin 40 mg orally daily
  - Metformin 1 g orally twice daily
  - Glimepiride 4 mg orally twice daily
  - Sitagliptin 100 mg orally daily
  - Co-Q 10 daily (OTC)
  - Multivitamin daily (OTC)

- **Allergies:**
  - None

- **Aversions:**
  - Pioglitazone (lower extremity edema)

Physical Exam

- Unremarkable, except for these pertinent findings:
  - Obesity
  - Acanthosis nigricans
  - Hepatomegaly
  - Negative for peripheral neuropathy
Questions to Address

• Would further oral therapy be beneficial for Brittany? Why or why not?
• What are the primary barriers to intensifying Brittany’s treatment regimen?
• At this stage of her life with diabetes, what does she need to understand about her illness, body, and medications?
• If injectable therapy is the next step, what is the best way to introduce this to Brittany?
Barriers to Injectables: The Patient/Partner/Caregiver Side of the Equation

• Pain and/or fear of injections
• Disease is bad/much worse and they have failed to control it
• Misattribution: bad outcomes in others who have used insulin
• Weight gain
• Loss of control of daily activities (eg, driving, occupation)
• Hypoglycemia
• Medication regimen complexity (multi-pill + injection)
• Loss of privacy (people observe insulin “equipment”)

Barriers to Injectables: The Clinician Side of the Equation

• Misperceptions
  – The need to advance treatment is never-ending (therapeutic fatigue)
  – Insulin: most appropriate for end-stage treatment
  – Patients don’t want to use injectables
• Reality-based concerns
  – Time demands of instructing patients about injections
  – Unfamiliarity with the variety of devices (eg, various pens)

• Knowledge gaps
  – Role of glucotoxicity in disease progression and therapeutic failure
  – Typical weight changes (gain) with insulin: misconceptions regarding insulin and appetite
  – Typical weight changes (loss) with GLP-1 RA: quartiles of weight changes expected
  – Familiarity with ADA/EASD and AACE guidelines
  – “If only patients would exercise and lose weight, then they wouldn’t need insulin”
Progressive β-Cell Dysfunction Is a Key Driver of Progressive Dysglycemia in T2DM

By the time of diabetes onset, up to 80% of β-cell function may be lost

Deteriorating β-cell function is partially driven by the incretin defect


Figure adapted from Kendall DM, et al. / Am J Med. 2009;122:S37-50.

Ominous Octet

Consequences of Delayed Intervention

Patients with HbA1C ≥ 7% not receiving IT within 1 year of diagnosis

Patients with HbA1C < 7% who received IT before 1 year of diagnosis

At 5.3 years, significantly increased risk of:
- MI, 67% (HR CI: 1.39, 2.01)
- Stroke, 51% (HR CI: 1.25, 1.83)
- HF, 64% (HR CI: 1.40, 1.91)
- Composite CVE, 62% (HR CI: 1.46, 1.80)

Insulin Initiation Delayed

- Kaiser Permanente Northwest patients, observational study
- N = 3,891 newly initiated on sulfonylurea/metformin
- Mean follow-up of 54.6 ± 28.6 months:
  - 41.9% added insulin
  - 11.8% were on maximum oral agents
- One-half of the sulfonylurea/metformin group had an HbA1C of ~9% for 3 years after some initial success
- Another 18% never achieved the first goal and continued oral agents for 30 months with an HbA1C of ~10%
Insulin vs Sulfonylurea in People With Newly Diagnosed T2DM: C-Peptide Response

- People newly diagnosed with T2DM were randomly assigned to the sulfonylurea glibenclamide (n = 26) or 70/30 NPH/soluble insulin (n = 23)
- 18 patients in the sulfonylurea group and 16 patients in the insulin group completed a 6-year follow-up
- People using sulfonylurea were more likely to lose insulin secretion than people on early insulin treatment
- Results demonstrate beneficial effects of insulin treatment early in the course of T2DM

Figure not available for PDF due to copyright restrictions. Please see the references below.

ADA 2018: Standards of Medical Care in Diabetes
AACE: Glycemic Control Algorithm


Individualizing HbA1C Targets for People With T2DM

Figure not available for PDF due to copyright restrictions. Please see the reference below.

What Happens Next for Brittany?

• She is offered intensification with basal insulin, but she declines because she just doesn’t feel right about taking insulin at her age
• No concerns about injections
• Stops sitagliptin and starts dulaglutide
  – But stops after 2 doses after getting sick at her son’s birthday barbecue
• Starts empagliflozin 10 mg
  – HbA1C remains at 8.2%, so empagliflozin is increased to 25 mg
  – Asked to return for follow-up in 3 months, at which point HbA1C is 8.0%

Diabetes Medications:
• Metformin 1 g PO BID
• Empagliflozin 25 mg PO QD
• Glimepiride 4 mg PO BID
• Sitagliptin 100 mg PO QD

Talking Points: When Is It Time for Brittany to Add Insulin?

• When have sulfonylureas outlived their usefulness?
• How best to control fasting glucose?
• Can Brittany adhere to daily injections?
• How to choose between reinstituting GLP-1 RA therapy vs talking through insulin: the value of shared decision making
  – Explore her fears about insulin, and try to erase old prejudices
  – Address her family history, realistic expectations of treatment options, and prompt glucose control
  – Do not use threatening outcomes
• There is no better time than today to initiate injectables
**When to Consider Insulin in a Person With T2DM**

- When a combination of noninsulin antihyperglycemic medications are unable to achieve HbA1C target
- Unacceptable side effects of other medications
- Hyperglycemia in a hospitalized patient
- “Severely” uncontrolled diabetes\(^a\)
- HbA1C > 8.0% on 3 OADs
- Choosing the appropriate insulin for the specific glycemic goals and timing is important

\(^a\)ADA: random glucose ≥ 300-350 mg/dL or HbA1C ≥ 10%-12%, with polyuria, polydipsia, weight loss, or ketosis. AACE: HbA1C > 9% with hyperglycemia symptoms.

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**Insulin Therapy in T2DM: Basic Facts**

- Basal insulin alone is able to achieve target HbA1C in ~50% of patients
- Initial starting dose can be 0.1-0.2 u/kg/d
- Can be prescribed with metformin + 1 or 2 additional noninsulin agents
- If basal insulin + OADs are unable to achieve target HbA1C in a patient, consider initiating GLP-1 RA, SGLT2 inhibitor, or prandial insulin
- If insulin is added, consider eliminating ineffective OADs
Types of Insulin

- **Ultra–rapid-acting analog:** Inhaled human insulin
- **Rapid-acting analogs:** Aspart, glulisine, lispro
- **Short-acting regular human insulin (soluble)**
- **Intermediate-acting NPH human insulin**
- **Long-acting basal insulin analogs:** Detemir, glargine, U300 glargine, degludec
- **Human insulin 70/30:** Premix NPH/regular
- **Premixed analogs:** Insulin lispro mix 75/25, 50/50
- **Biphasic insulin aspart 70/30**
- **Rapid-acting analogs:** Aspart, glulisine, lispro
- **Short-acting regular human insulin (soluble)**
- **Intermediate-acting NPH human insulin**
- **Long-acting basal insulin analogs:** Detemir, glargine, U300 glargine, degludec
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- **Premixed analogs:** Insulin lispro mix 75/25, 50/50
- **Biphasic insulin aspart 70/30**

**Duration of action**
- U300 glargine—36 hours
- Degludec—42 hours

Glycemic Variability: An Issue When Using Exogenous Insulin

- Increases risk of hypoglycemia
- Drives long- and short-term complication rates
- Decreases adherence
- Reduces likelihood of patients successfully achieving their glycemic goals
- Confuses patients and clinicians


When to Consider GLP-1 RA Rather Than Insulin

- When postprandial glucose control is inadequate
- In the setting of severe insulin resistance
- When significant weight loss is a medically essential goal
- When weekly rather than daily dosing would improve adherence
- When hypoglycemia poses a significant health risk (eg, cardiovascular risk)
- In those who fear insulin

Lixisenatide vs Liraglutide as Add-On to Optimized Insulin Glargine ± Metformin

Responses at End of 28 Weeks of Therapy

Lixisenatide 20 mcg (n = 46) vs Liraglutide 1.8 mg (n=46)

- HbA1C, %
- FPG, mg/dL
- Body Weight
- Daily Insulin Dose

Lixisenatide 20 mcg: -0.6\(^{a}\), -1.6\(^{b}\)
Liraglutide 1.8 mg: -0.7\(^{a}\), -2.4\(^{a}\)

\(^{a}\)P < .001, \(^{b}\)P < .05 for change from baseline.
Why Not Just Add Sitagliptin?: GLP-1 RA Activity Is Higher With GLP-1 RAs Than With DPP-4 Inhibitors


Figure not available for PDF due to copyright restrictions. Please see the reference below.

FDA-Approved GLP-1 RAs

- **Albiglutide**
  - 30-50 mg once weekly
- **Dulaglutide**
  - 0.75-1.5 mg once weekly
- **Exenatide**
  - 5-10 mcg twice daily
  - 2 mg once weekly
- **Liraglutide**
  - 0.6-1.8 mg daily
  - 0.6-3 mg daily (weight loss indication)
- **Lixisenatide**
  - 10-20 mcg daily
- **Semaglutide**
  - 0.25-1 mg weekly

*Manufacturing and sale to be discontinued in July 2018.*
Comparing GLP-1 RAs: Shorter-Acting vs Longer-Acting Formulations

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<th>Shorter Acting</th>
<th>Longer Acting</th>
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<tr>
<td></td>
<td>lixisenatide</td>
<td>liraglutide, semaglutide</td>
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<tr>
<td>Half-life</td>
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<td>12 hours to several days</td>
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Effects

- FBG reduction
- Postprandial hyperglycemia reduction
- Fasting insulin secretion stimulation
- Glucagon secretion
- Weight reduction
- Potential for nausea

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GLP-1 RAs Demonstrate a Low Risk of Hypoglycemia

- With MET
- With Basal Insulin


*aManufacturing and sale to be discontinued in July 2018.

GLP-1 RAs Demonstrate a Low Risk of Hypoglycemia

- Overall Hypo, %

**In combination with or without metformin and/or a TZD.
**In combination with or without metformin.

Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda.
Only About One-Third of Patients Are Adherent to GLP-1 RAs

- A claims database study of 1,321 patients with T2DM who were treated with liraglutide once daily
- Adherence defined as PDC ≥ 0.8

Patient Education Talking Points for GLP-1 RA

- Instruct on good injection technique
- Discuss GI disturbances; inform patients that they should start with small meals and eat slowly
- Explain that it may cause hypoglycemia when used with sulfonylureas or insulin
- Exenatide twice daily or liraglutide: prime or set-up pen device only once when medication is first started
- Explain that patients should store GLP-1 RAs in the refrigerator until pen is in use, then keep at room temperature
- Discuss risk of pancreatitis and MTC when initiating a GLP-1 RA
- Discuss signs and symptoms of pancreatitis
Brittany: 6 Months Later

• Advised to discontinue glimepiride
• Started on liraglutide 0.6 mg daily for 1 week and then titrated to 1.2 mg daily. She was tolerating this at her 3-month follow-up visit
• At her 6-month follow-up visit:
  – HbA1C remains at 7.4%
  – Complains of occasional hypoglycemic episodes
  – Confused about how her sugar can be so high in the morning (ranges from 160-220 mg/dL) but is low at 3 pm when she is driving to pick up her children

Benefits and Limitations of GLP-1 RA Used in Conjunction With Basal Insulin
Rationale for GLP-1 RA and Insulin Combination

• Can optimize glucose control
• Helps lessen the adverse effects associated with insulin alone
• Clinical studies have shown beneficial effects compared with insulin alone:
  • Improvements in glycemic control
  • Weight loss
  • Low incidence of hypoglycemia
  • Reduction in insulin use when added to existing insulin therapy

Combining GLP-1 RA and Basal Insulin

Basal Insulin Analogs
• Simple to initiate
• Control nocturnal hyperglycemia and FPG
• Lower hypoglycemia risk than NPH
• Can cause weight gain
• Achieve HbA1C target in ~50%

GLP-1 RAs
• Simple to initiate
• Can control FPG and PPG
• Do not impair α-cell response to hypoglycemia (reduce risks of severe hypoglycemia)
• Weight-lowering
• Achieve HbA1C target in ~50%

Potential for Better Overall HbA1C Control

Recommendations for GLP-1 RA Use in Combination With Basal Insulin

- GLP-1 RA may be used in combination with basal insulin in patients who do not reach their glycemic target with 2-3 glucose-lowering medications
  - If taking a sulfonylurea, consider discontinuing or reducing the dose of sulfonylurea
- If adding GLP-1 RA to basal insulin, consider reducing basal insulin dose by 10%-20% if HbA1C < 8% or fasting BGM near normal
  - Thereafter, adjust basal insulin dose based on self-monitoring of blood glucose
- Monitor for hypoglycemia

Fixed Combinations of GLP-1 RAs and Insulin

- **iDEG-LIRA**
  - **Indication:** an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin or liraglutide
  - **Dosing:**
    - Starting dose 16 units daily
    - Maximum dose 50 units daily
  - **Common adverse effects:** nasopharyngitis, headache, nausea, diarrhea, increased lipase, and upper respiratory tract infection
  - **Warning:** risk of thyroid C-cell tumors
  - **Warnings and precautions:** hypoglycemia

- **iGLAR-LIXI**
  - **Indication:** an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin or lixisenatide
  - **Dosing**
    - Starting dose 15 units daily if inadequately controlled on < 30 units of basal insulin or on lixisenatide
    - Starting dose 30 units if inadequately controlled on 30-60 units of basal insulin
    - Maximum dose 60 units daily
  - **Common adverse effects:** hypoglycemia, allergic reactions, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, headache
  - **Warnings and precautions:** hypoglycemia
Basal Insulin/GLP-1 RA Fixed-Ratio Combinations

- iDEG-LIRA was noninferior to DEG and superior to LIRA (26-week, open-label, treat-to-target RCT; N = 1,663 [insulin naïve])
- iGLAR-LIXI was superior to iGLAR (24-week, open-label, treat-to-target RCT; N = 323 [insulin naïve])

- ≤ 3 severe hypoglycemic episodes per group
- Lower rate of hypoglycemia for LIRA vs iDEG or iDEG-LIRA (overall and nocturnal)
- Lower rate of hypoglycemia for iGLAR-LIXI than for iGLAR (overall)

iDEG-LIRA: Hypoglycemia Rate by Baseline HbA1C Category

Figure not available for PDF due to copyright restrictions. Please see the references below.
iGLAR-LIXI: Hypoglycemia Rate by HbA1C at Screening

Figure not available for PDF due to copyright restrictions. Please see the reference below.


GLP-1 RA/Basal Insulin Fixed-Ratio Combination

• Practical considerations:
  – A reasonable choice for patients on GLP-1 RA or basal insulin and not at goal
  – Both medications in a once-daily administration may improve adherence for both medications vs taking the medications individually
  – Dose range is based on the units of insulin but is limited by the maximum dose of GLP-1 RA
  – The same risks/benefits and contraindications apply to the combinations as to the individual medications
  – Insurance coverage remains a challenge for many
Helping Brittany Experience Glycemic Success

• Uncomfortable with 2 shots of insulin and GLP-1 RA but open to 1 shot of a fixed-dose combination
• Stops liraglutide and starts lixisenatide/glargine at 15 units
• At 3 months:
  – Titrated up to 1 dose daily of glargine/lixisenatide at 60 units
  – Has improved confidence in her diabetic well-being and control
  – No longer has any hypoglycemia
  – More motivated to work on long-term health
• Unfortunately, her work hours make it difficult for her to see a CDE, and her physician cannot provide any additional resources

The Hours Outside of Clinic

How can we better empower our patients like Brittany to be active members of their own care?

Diabetes Medications:
- Lixisenatide/glargine 60 units QD
- Metformin 1 g PO BID
- Liraglutide 1.2 mg SQ daily
- Empagliflozin 25 mg PO QD
- Glimepiride 4 mg PO BID
- Sitagliptin 100 mg PO QD
Patient Engagement Process

• Set the stage:
  – Invite the patient to participate
  – Present options
  – Provide information on risks and benefits
  – Assist patient in evaluating goals
  – Facilitate deliberation and decision making
  – Assist patients to follow through on the decision

How Can We Improve Patient Engagement Outside of the Clinic?

• Patients with chronic conditions spend:
  – Only a few hours each year with a healthcare provider
  – 5,000 hours each year engaged in everything else:
    ▪ Deciding to follow medical advice
    ▪ Deciding to take their medications
    ▪ Deciding what to eat and drink
    ▪ Making other decisions that affect their health

Examples to Enhance Patient Engagement

- **Peer mentoring**
  - Program in which African American veterans with diabetes talked to a peer mentor at least once a week
  - Associated with greater reductions in HbA1C levels compared with usual care and financial incentives

- **Digital and personal coaching resources**
  - Program that combined digital health and human coaching for older adults at risk of diabetes
    - Associated with improved health, weight, and well-being
  - Remote digital coaching program for patients with uncontrolled asthma
    - Associated with improvements in mental status, outpatient exacerbations, body weight, and Asthma Symptom Utility Index

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Summary: Overcoming Clinical Inertia

- Delay in achieving glycemic control leads to adverse glycemic legacy, increased complications, and long term β-cell dysfunction
- Patient engagement in therapeutic decision making often significantly enhances patient outcomes
- Many barriers to injectables exist but can be overcome through teaching and relationship building with your patient
- GLP-1 RAs are an effective means of using endogenous insulin for postprandial glycemia, and basal insulin is an effective means of using exogenous insulin to normalize fasting hyperglycemia
- Combined injectable therapy is an effective way of addressing hyperglycemia while increasing adherence and decreasing fasting and postprandial hypoglycemia
Abbreviations and Acronyms

- AACE = American Association of Clinical Endocrinologists
- ADA = American Diabetes Association
- BGM = blood glucose monitoring
- BMI = body mass index
- CDE = certified diabetes educator
- Co-Q = coenzyme Q10
- CVE = cardiovascular endpoint
- DPP-4i = dipeptidyl peptidase-4 inhibitor
- FBG = fasting blood glucose
- FPG = fasting plasma glucose
- eGFR = estimated glomerular filtration rate
- GI = gastrointestinal
- GLP-1 RA = glucagon-like peptide-1 receptor agonist
- HbA1C = glycated hemoglobin
- HCTZ = hydrochlorothiazide
- HDL = high-density lipoprotein
- HF = heart failure
- HTN = hypertension
- iDEG-LIRA = insulin degludec + liraglutide
- iGLAR-LIXI = insulin glargine + lixisenatide
- IT = treatment intensification
- MI = myocardial infarction
- MTC = medullary thyroid carcinoma
- NPH = neutral protamine Hagedorn
- NS = not significant
- OAD = oral antidiabetic drug
- OTC = over the counter
- PDC = proportion of days covered
- PPG = postprandial plasma glucose
- PVD = peripheral vascular disease
- p-y = patient-year
- RCT = randomized controlled trial
- SGLT2i = sodium-glucose cotransporter 2 inhibitor
- SU = sulfonylurea
- T2DM = type 2 diabetes mellitus
- TZD = thiazolidinedione