SCENES AND SEMINARS ON
HYPOGLYCEMIA MANAGEMENT IN DIABETES
MULTIDISCIPLINARY APPROACHES TO
IMPROVING SAFETY FOR PATIENTS WITH DIABETES

FEATURING:
Etie Moghissi, MD, FACP, FACE—Program Chair
Davida F Kruger, MSN, ADM-BC, BC-ADM
Luigi F Meneghini, MD, MBA

Recognizing Hypoglycemia
From Blood Glucose Monitoring Records

This activity is co-provided/co-sponsored by the American Association of Clinical Endocrinologists and the Institute for Medical and Nursing Education, Inc.

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Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Activity Overview and Format

This live webinar series is designed to address the many complexities of hypoglycemia management that clinicians frequently encounter in treating patients with diabetes, including identification of hypoglycemia from blood glucose monitoring data, appropriate use of basal and prandial insulin therapy, recognition of hypoglycemia unawareness, and special considerations for hypoglycemia avoidance in young children, pregnant women, and older adults.

The content for this series is divided into 3 unique live webinars, each featuring a realistic case scenario typical of patients with diabetes commonly seen in clinical practice. With each webinar, participants will have the opportunity to interact with expert faculty during live question-and-answer sessions via an online web portal or telephone.

Program Topics

- Blood glucose monitoring technology
- Blood glucose monitoring patterns
- Stepwise initiation of insulin
- Glycemic variability and hypoglycemia

Monitoring of blood glucose patterns is a cornerstone of diabetes management, especially for insulin-treated patients, yet few clinicians have had formal training in this critical skill. This webinar is designed to help clinicians interpret blood glucose monitoring records in several formats, recognize and avoid hypoglycemia, and address glycemic variability. Insulin therapy considerations in type 2 diabetes will emphasize recent guidelines for initiating insulin as well as advancing beyond basal insulin regimens.
Target Audience

The proposed activity is intended for physicians, nurse practitioners, physician assistants, nurses, diabetes educators, pharmacists, and other interested healthcare professionals who treat and educate patients with diabetes.

Educational Objectives

At the conclusion of this webinar, participants should be able to:
- Recognize hypoglycemia from different types of blood glucose monitoring data
- Explain how physiological counterregulatory mechanisms, such as the dawn phenomenon and Somogyi effect, occur and how to avoid them
- Describe blood glucose monitoring techniques to identify asymptomatic hypoglycemic episodes

Faculty

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University of California, Los Angeles
Los Angeles, California

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Henry Ford Health System
Detroit, Michigan

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Division of Endocrinology
University of Texas Southwestern Medical Center
Executive Director
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Dallas, Texas
Dr. Moghissi is a Clinical Associate Professor of Medicine at the University of California, Los Angeles and has a private practice in Marina del Rey, California. As a native of Shiraz, Iran, she earned her medical degree from Pahlavi University School of Medicine in Shiraz. She completed an internal medicine residency at St. Luke’s-Roosevelt Hospital at Columbia University in New York City and a fellowship in endocrinology at the University of Southern California in Los Angeles. She is board certified by the American Board of Internal Medicine and the American Board of Endocrinology and Metabolism.

Dr. Moghissi coauthored the 2011 American Association of Clinical Endocrinologists (AACE) Comprehensive Diabetes Guidelines and currently serves as the Chair of AACE’s Diabetes Resource Center Task Force. She chaired and was the lead author of the 2009 AACE/American Diabetes Association (ADA) Consensus Statement on Inpatient Glycemic Control. Dr. Moghissi was also Co-Chair of the AACE Inpatient Diabetes Consensus Conference and Position Statement (2004) and the AACE/ADA Inpatient Diabetes “Call to Action” Consensus Conference and Position Statement (2006). In 2007, she led the effort to create the Inpatient Glycemic Control Resource Center on AACE’s website. Her efforts have been instrumental in driving a major shift in optimizing the care of hospitalized patients with diabetes.

Dr. Moghissi was the Vice President of the AACE in 2010, President-Elect in 2011, and Past President of its California chapter. Her areas of interest include direct patient care and teaching in the field of diabetes, and she has lectured extensively on these topics on both the national and international levels.
Ms Kruger has been a Certified Nurse Practitioner in diabetes for the past 31 years at Henry Ford Health System in Detroit, Michigan. Her role includes both clinical practice and research. She is board certified by the American Nurses Credentialing Center in both primary care and advanced diabetes management. She is Past Chair of the American Diabetes Association’s (ADA’s) Research Foundation and has served on the ADA’s Research Policy Committee. Ms Kruger is also Past President of Health Care and Education of the ADA. She served as Editor of Diabetes Spectrum from 2005 to 2008. Presently, she serves as Editor-in-Chief of Clinical Diabetes. Ms Kruger has been a principal investigator on numerous research projects and has written widely on diabetes care, authoring the second edition of The Diabetes Travel Guide (2006). Her awards include the Florence Nightingale Award for Excellence in Research, the ADA’s Rachmiel Levine Medal for Distinguished Service, the ADA’s Ross Hickey Award for Outstanding Service in Diabetes Research Funding, and the ADA’s Wendell Mayes, Jr Award for Lifetime Service.
A native of Italy who grew up in Liberia (West Africa), Dr Meneghini emigrated to the United States in 1979 and attended Emory University and its School of Medicine, graduating in 1988. He moved to Miami to complete training in Internal Medicine and subsequently a fellowship in Endocrinology, Diabetes & Metabolism at the University of Miami/Jackson Memorial Hospital. He was offered a position as Assistant Professor of Clinical Medicine (Clinical Educator Track) in 1993 at the University of Miami School of Medicine. In 2000 he graduated valedictorian in his Executive MBA class (University of Miami) and made active use of his dual training in medicine and business to grow and develop clinical operations within the University of Miami Medical Group. Following a 20-year tenure at the University of Miami Miller School of Medicine, where he was Professor of Clinical Medicine and Director of the Kosow Diabetes Treatment Center, Dr Meneghini is currently a Professor of Internal Medicine in the Division of Endocrinology at the University of Texas Southwestern (UT Southwestern) Medical Center, Dallas, Texas, and is Executive Director of the Parkland Health and Hospital System Global Diabetes Program, also located in Dallas.

Dr Meneghini’s primary interests lie in improving the lives of patients with diabetes through the application of cutting edge drug therapies and technologies, and the implementation of these management strategies through patient and professional education activities. At the beginning of the millennium, Dr Meneghini was instrumental in translating and adapting an innovative European educational approach to intensive insulin management (Mastering Your Diabetes), which places the expertise and problem solving skills in the hands of the patient with diabetes. He has been involved in the development of treatment algorithms for glycemic control of type 1 and type 2 diabetes. At UT Southwestern he is charged with implementing a registry-based chronic care model and exploring opportunities for leveraging this infrastructure to optimize population-based health management and translation research.

Dr Meneghini is well recognized for his clinical expertise in the management of type 1 and type 2 diabetes, both locally and internationally. He has been selected for various awards over the years including Best Doctors, Guide to America’s Top Physicians, Florida’s Best Doctors, Strathmore’s Who’s Who, Best Doctors in America and Guide to America’s Top Physicians, to name a few.

Dr Meneghini is a frequent lecturer, and has published numerous articles on diabetes in peer-reviewed medical journals. He is actively involved in clinical research, much of which revolves around the application of insulin formulations and algorithms in both the outpatient and hospital setting. He has presented numerous projects at the Scientific Sessions of the American Diabetes Association and the European Association for the Study of Diabetes, many of which involved mentoring of physicians in training and junior faculty.
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Case Scenario Introduction—Pam and the Problematic Postprandial Pattern

Etie Moghissi, MD, FACP, FACE
Program Chair
Clinical Associate Professor
University of California, Los Angeles
Los Angeles, California

Case Study: Pam
Presentation

History
- Female patient, aged 64 years
- T2DM, 13 years
- Hypertension, 18 years
- Dyslipidemia, 14 years
- Height: 5’6”
- Weight: 172 lb
- BMI: 27.8 kg/m²

Current Medications
- Metformin 1000 mg bid
- Pioglitazone 15 mgid
- Basal insulin analogue 23 units at bedtime
- ARB, CCB, HCTZ
- Statin

Laboratory Results
- In-office glucose = 110 mg/dL
- A1C = 6.8%
- BP: 135/95
- Lipids: normal
- eGFR = 50 mL/min
- LFTs: normal

- For the last 2 months, Pam has noticed that her morning glucose levels have been high and go even higher after a low-carbohydrate breakfast
- Pam has self-titrated her bedtime basal insulin dose from 18 units to 23 units, but her morning SMBG levels remain increased
- She explains that she doesn’t like to bother your nurse with minor problems, which is why she hasn’t called about the dose adjustments
- Upon questioning, she mentions that she feels unexpectedly tired when she gets up in the morning
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

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Certified Nurse Practitioner
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Henry Ford Health System
Detroit, Michigan

Talk Outline

- Hypoglycemia and patient safety
- Blood glucose monitoring technology
- Blood glucose pattern management

HYPOGLYCEMIA AND PATIENT SAFETY
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Hypoglycemia Is a Significant Patient Safety Priority

- Current treatment guidelines prioritize prevention of hypoglycemia.1,2
- Improving patient safety is a key national healthcare quality priority.3
- Hypoglycemia—including severe hypoglycemia—occurs in all types of diabetes.4
- Any degree of hypoglycemia impairs QOL.5
- QOL worsens with increasing hypoglycemia severity.6
- Hypoglycemia is associated with an increased risk of morbidity, mortality, lost productivity, and higher healthcare costs.5
- Inpatient hypoglycemia increases the risk of short-term readmission by 20%.7

Definition and Classification of Hypoglycemia

- Low plasma glucose could lead to potential harm.
- Alert value for hypoglycemia: BG ≤ 70 mg/dL.
- Allows time to take action to prevent severe episode.
- Initial activation of counterregulatory response.
- Inactivation of CR hormone response with repeated events.
- Risk is higher in patients treated with SU, glinides, or insulin.

<table>
<thead>
<tr>
<th>Type</th>
<th>Assistance Needed</th>
<th>Symptoms</th>
<th>Documented Plasma Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Documented symptomatic</td>
<td>✓</td>
<td>≤ 73 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td>≤ 73 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Probable symptomatic</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudohypoglycemia</td>
<td>✓</td>
<td>&gt; 73 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors for Hypoglycemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions Associated With Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>Increasing duration of diabetes</td>
</tr>
<tr>
<td></td>
<td>Increasing duration of insulin therapy</td>
</tr>
<tr>
<td>Behavioral factors</td>
<td>Missed or irregular meals, exercise</td>
</tr>
<tr>
<td></td>
<td>Recent hospitalization</td>
</tr>
<tr>
<td>Impaired drug clearance</td>
<td>Hepatic failure, hypothyroidism</td>
</tr>
<tr>
<td>Impaired counterregulatory capacity</td>
<td>Adipsos disease, growth hormone deficiency, hypoglycemia</td>
</tr>
<tr>
<td>Decreased endogenous glucose production</td>
<td>Prior hypoglycemia, cognitive impairment</td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>Decreased renal excretion of SUs (aspirin, allopurinol)</td>
</tr>
<tr>
<td></td>
<td>Displacement of SUs from albumin (aspirin, warfarin, trimethoprim)</td>
</tr>
<tr>
<td>Medication errors</td>
<td>Insulin or SU doses are excessive, ill-timed, or of the wrong type</td>
</tr>
<tr>
<td></td>
<td>Use of sliding-scale insulin or glyburide in long-term care settings</td>
</tr>
</tbody>
</table>
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

BLOOD GLUCOSE MONITORING TECHNOLOGY

Blood Glucose Monitoring Is a Cornerstone Technology for Identifying and Preventing Hypoglycemia

- SMBG is effective, provided that:
  - Both patients and HCPs know how to interpret readings and take appropriate action
  - SMBG is performed in a structured format

- Structured SMBG means that:
  - Readings are performed according to a prespecified pattern
  - Readings are used to guide treatment

- Structured SMBG results in A1C reduction of about 0.2% per test (up to 5 tests/day)
  - Individualize targets, timing, and frequency of SMBG

- Efficacy demonstrated in T1DM and in T2DM, regardless of treatment regimen
- Risk of hypoglycemia is greatest with insulin and insulin secretagogues

Structured SMBG Options in T2DM

Less Intensive Monitoring (staggered monitoring)

More Intensive Monitoring (episodic intensive monitoring)

Improvements in average blood glucose levels have been found in studies in which structured blood glucose monitoring was used as part of an intervention that included education and collaborative care.

Effective Glucose Monitoring Requires Review and Interpretation by Clinicians and Patients

- Patients need to know their individual blood glucose goal(s), benefits of monitoring, and when and why to check.¹
- Clinicians need to review blood glucose trends, medications, meals, and activities with patient—information not available from a cursory glance at their A1C.²,³
- Clinicians should coach patients on actions that may help improve blood glucose control.⁴
- Fabrication of SMBG readings is common: meter downloads may clarify discrepancies from paper records.³

SMBG Record Illustrating Wide Glycemic Variation

Continuous Glucose Monitoring (CGM) Can Catch Blood Glucose Trends That SMBG May Miss

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Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Recommendations for Use of CGM

- Overview
  - See trends in blood glucose readings
  - Does not replace SMBG
  - Used for both T1DM and T2DM

- Types
  - Personal
  - Professional

- Indications
  - Frequent hypoglycemia
  - Glycemic variability considered excessive, potentially disabling, or life threatening
  - Need to improve glycemic control or maintain A1C without increasing risk of hypoglycemia
  - During preconception and pregnancy
  - Hypoglycemia unawareness

Record courtesy of D. Roeger, Patient MD.

BLOOD GLUCOSE PATTERMANAGEMENT

Structured SMBG Reduces A1C in T2DM: STeP Trial Pattern Management

- 7-point BG profiles collected over 3 days
- Data used by patient AND provider
- Pattern management priorities:
  1. Hypoglycemia
  2. Fasting/preprandial hyperglycemia
  3. Postprandial hyperglycemia
- Abnormality occurring on 2 of 3 days at the same time of day must be addressed

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2946345/
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

**Priority 1—Correct Hypoglycemia**

What to look for: any BG readings below target range, especially at night; may occur even if BG is too high at other times of the day. Potential causes: medication doses too high, exercise without sufficient food intake, skipping meals.

**Priority 2—Fix the Fastings ( > 110 mg/dL)**

What to look for: most BG values higher than upper limit of target range. Potential causes: medication doses too low or skipped.

**Priority 3—Postprandial Hyperglycemia**

What to look for: FPG within range, but PP too high ~ 1-2 h after meals. Potential causes: progression of T2DM, medication that only addresses fasting glucose, large meals, high glycemic index foods, lack of exercise.
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Helpful Resources for Pattern Management

- Downloadable paper chart for structured testing
- Downloadable apps for glucose monitoring
- Patient information on hypoglycemia prevention and treatment:
- More training on pattern management for HCPs:

AVOIDING EXCESSIVE BASAL INSULIN DOSES

Aggressive Basal Dose Titration May Increase Severe Hypoglycemia Without Improving A1C

- Mean Insulin glargine dose, units/day
- Mean A1C, %
- Severe hypoglycemia, rate/year

Incidence of severe hypoglycemia increased with higher insulin doses, with only a small reduction in A1C

24-week randomized study, n=463.
Scenes and Seminars on Hypoglycemia Management in Diabetes

Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Elevated Prebreakfast Glucose May Be Due to the Dawn Phenomenon or Somogyi Effect

Dawn Phenomenon
- Occurs in T1DM and non-insulin-treated T2DM
  - 2-4% T1DM
  - 18-50% T1DM
- Insulin secretions naturally decline between 3:00-5:00 AM, raising BG
- Cortisol naturally increases before awakening, further raising BG
- Look for high-normal BG at 3:00-5:00 AM and elevated prebreakfast glucose
- If found, do not increase bedtime basal insulin dose!

Somogyi Effect
- Occurs in T1DM and insulin-treated T2DM
  - 12-57% T1DM and T2DM
  - 18% T1DM
- Sometimes called “rebound hyperglycemia”
- Results from excessive bedtime insulin dose, triggering counterregulatory response
- Look for high BG at 3:00-5:00 AM and elevated prebreakfast glucose
- If found, do not increase bedtime basal insulin dose!

Consider using long-acting insulin analogues instead of NPH insulin or using insulin pumps in these patients

Meal Composition Effects on PPG

- Rice pudding with sugar and cinnamon: 271 kcal
- Toast, honey, jam, curd cheese, orange juice: 252 kcal
- Kidney beans, wholemeal bread, salad, cheese: 750 kcal
- Grilled salmon, broccoli, carrots, wild rice, cream: 778 kcal

Meal composition alters PPG > 40 to 50 mg/dL in healthy individuals

Clinical Pearls
- Avoiding hypoglycemia is a higher clinical priority than “fixing the fasting level”!
  - 70 mg/dL is the alert level for intervention
  - Address hypoglycemia before hyperglycemia
- Blood glucose monitoring is a cornerstone tool for diabetes management, regardless of diabetes type or treatment regimen
- Both SMBG and CGM require regular review and use by patients and providers for effective use
  - Become familiar with reading data in different formats
- Excessive basal insulin doses (in T2DM and some T1DM) can trigger counterregulatory responses, resulting in paradoxically elevated glucose levels
Hypoglycemia and Glycemic Variability

Luigi F Meneghini, MD, MBA
Professor of Internal Medicine
Division of Endocrinology
University of Southwestern Medical Center
Executive Director
Parkland Health and Hospital System
Global Diabetes Program
Dallas, Texas

Talk Outline

- Glycemic variability
  - Hypoglycemia + wide variability = increased risk
  - Link to diabetes complications
- Treatment regimens to reduce hypoglycemia and glycemic variability
  - Stepwise insulin therapy
  - Insulin combination therapy

A1C and Glycemic Variability

A1C = 6.8%
Mean BG (SD) = 147 (72) mg/dL

A1C = 6.8%
Mean BG (SD) = 151 (92) mg/dL

Glycemic variability describes mean change over time/1,4
- BG: changes over 24 hours/4
- A1C: changes over months to years/1,2

Records courtesy of L. S. Hirsch, MD
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

**Blood Glucose Variability Is Typically Higher in Individuals With T1DM Than in Those With T2DM**

<table>
<thead>
<tr>
<th>T1DM, 29 y, BMI = 31</th>
<th>T2DM, 65 y, BMI = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph showing blood glucose variability" /></td>
<td></td>
</tr>
</tbody>
</table>

With increasing disease duration, the amount of variability in T2DM more closely resembles that seen in T1DM.


**Factors Contributing to Glycemic Variability**

<table>
<thead>
<tr>
<th>Glucose Monitoring</th>
<th>Injection Device</th>
<th>Injection</th>
<th>Insulin Preparation</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ± 15% variability</td>
<td>• Syringe vs pen</td>
<td>• Site</td>
<td>• Human vs analogues</td>
<td>• Insulin temperature</td>
</tr>
<tr>
<td>• Technique</td>
<td>• CSII</td>
<td>• Depth</td>
<td>• Rapid vs delayed</td>
<td>• Food intake</td>
</tr>
<tr>
<td>• Reporting</td>
<td></td>
<td>• Volume</td>
<td>• Suspension vs soluble</td>
<td>• Activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Temperature</td>
<td></td>
<td>• Stress/Sickness</td>
</tr>
</tbody>
</table>

**Glycemic Variability Is Associated With Increased Risk of Complications and Mortality in Diabetes**

- Greater variability may be associated with a higher incidence of retinopathy, nephropathy, and CV mortality.
- Glycemic variability may be an additional risk factor for morality in patients with hypoglycemia.
- Wide glycemic variability is more common in patients:
  - Aged < 60 years old
  - With longer duration of diabetes (T1DM and T2DM)
  - With coronary artery disease

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Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Glycemic Variability Is Associated With the Highest Mortality Risk in Critically Ill Patients With The Lowest Mean Glucose

Patients with the greatest variability had higher risk of mortality independently of overall glucose level

Treatment Conundrum in T2DM

β-cell failure

Insulin replacement needed

Increasing disease duration

Reduced glucagon secretion in response to hypoglycemia

Increased hypoglycemia risk

STEPWISE INSULIN MANAGEMENT TO REDUCE HYPOGLYCEMIA AND GLYCEMIC VARIABILITY
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Algorithm for Adding/Intensifying Insulin

**START** Basal (long-acting insulin)
- Add basal
- TDD: 0.8-1.2 U/kg

**INTENSIFY** (prandial control)
- Add GLP-1RA or TZD
- Add prandial insulin

Add GLP-1RA or TZD:
- TDD: 30-50 U/kg
- Titrate until hypoglycemia
- Monitor serum glucose

**Scene 3**
- **Hypoglycemia Goal**
  - **Prandial glucose**:
    - FPG: 130 mg/dL, Oral: 84 mg/dL
    - FPG: 180 mg/dL, Oral: 150 mg/dL
  - Prandial: 130 mg/dL, Oral: 95 mg/dL
  - Prandial: 150 mg/dL, Oral: 100 mg/dL

**During T2DM**

**HCPs need to know when to stop uptrating basal insulin**

**Indication 1**: FPG is in range
- Individual is meeting their FPG target, but not other glycemic targets, on basal insulin
- FPG with basal insulin is within target range, but PPG is persistently elevated (>180 mg/dl)
- HbA1c is above target despite normal FPG with basal insulin if FPG readings are not available

**Indication 2**: Basal insulin dose is increasing to 0.5 to 1.0 U/kg/d

**Indication 3**: Further increases in basal insulin result in hypoglycemia

**Insulin Therapy Strategies for Addressing Beta-Cell Failure in T2DM When Basal Insulin is Insufficient**

<table>
<thead>
<tr>
<th>Single prandial dose</th>
<th>OPAL</th>
<th>Premixed insulin therapy</th>
<th>4T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential prandial doses</td>
<td>STEPulse</td>
<td>FullSTEP</td>
<td>OSIRIS</td>
</tr>
<tr>
<td>BBT (full prandial coverage)</td>
<td>4T</td>
<td>OSIRIS</td>
<td>Adjust-to-target</td>
</tr>
</tbody>
</table>

**GLP-1 RA instead of prandial insulin**
- BEGIR (NCT01385361)
- 4B

**Harmony 6**

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Scenes and Seminars on Hypoglycemia Management in Diabetes

Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Intensifying Insulin Therapy in T2DM: Basal-Bolus vs Stepwise Insulin Therapy

- Basal and prandial doses are used from initiation of therapy
  - 1-2 basal doses/day
  - 1 prandial dose with each meal
  - 4-6 daily injections total
- Also appropriate for T1DM

Stepwise Insulin Therapy is Associated With Less Hypoglycemia Than Basal-Bolus Therapy

- Stepwise insulin caused less hypoglycemia than BBT
- Stepwise insulin was equally as effective as BBT

Steps for adding prandial insulin:
1. Start 4-6 units of rapid-acting analogue before largest meal
2. Adjust prandial insulin dose to target BG levels
3. Stop if not goal, add 2nd prandial dose before 2nd largest meal
4. Continue process until A1C is at goal or patient is on full basal-bolus

Stepwise Insulin Therapy Is Associated With Less Hypoglycemia Than Basal-Bolus Therapy

- Stepwise insulin caused less hypoglycemia than BBT
- Stepwise insulin was equally as effective as BBT
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

### Patients With T2DM May Be Able to Self-Titrate Insulin Doses Effectively and Safely

<table>
<thead>
<tr>
<th>Study</th>
<th>ATLANTUS1</th>
<th>PREDICTIVE 3032</th>
<th>START3</th>
<th>AUTONOMY4</th>
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<tbody>
<tr>
<td>Insulin type</td>
<td>Basal</td>
<td>Basal</td>
<td>BBT</td>
<td>Prandial</td>
</tr>
<tr>
<td>N</td>
<td>4588</td>
<td>5604</td>
<td>316</td>
<td>531 and 5814</td>
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<tr>
<td>Comparisons</td>
<td>Self-adjusted vs clinician-adjusted dosing</td>
<td></td>
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</tr>
<tr>
<td>Efficacy</td>
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<td>No difference</td>
<td>No difference</td>
<td>Nodifference</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>Nodifference</td>
</tr>
<tr>
<td>Weight gain</td>
<td>No difference</td>
<td>No difference</td>
<td>Clinician-adjusted better</td>
<td>Mixed results5</td>
</tr>
</tbody>
</table>

* Two independent studies of the same protocol; 1. Study 1, basal-glycemic results in significantly lower weight gain than BBT (2.2 kg vs 3.2 kg; P < 0.05); study 2, no difference (P > 0.05). 2. Morello et al, Diabetes Care 2011;33:952-957. 3. Halle M, et al., Diabetes Care 2013;36:364-369. 4. Selman SJ, et al, Diabetes Care 2014;37:1032-1039.

### INSULIN COMBINATION THERAPY TO REDUCE HYPOGLYCEMIA

### Reducing the Risk of Hypoglycemia With Insulin Combination Therapy

Combination therapy in T1DM is currently limited to pramlintide
- Improves glycemic control, reduces glycemic variability, and reduces weight gain
- Increases risk of hypoglycemia
- Injected with every meal cannot mix in same syringe as insulin
- Approved for use in T2DM in patients treated with prandial insulin

Many other agents are approved for combination therapy with insulin in T2DM
- Sulfonylurea
- Metformin
- Pioglitazone
- DPP-4 inhibitors
- GLP-1RAs
- SGLT2 inhibitors

Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Complementary Actions of Agents Associated With a Low Risk of Hypoglycemia With Insulin Therapy

Insulin

- Hepatic glucose production
- Insulin sensitivity
- Insulin secretion
- Glucagon secretion
- Weight neutral
- Insulin sensitivity
- Glucagon secretion
- Safety
- Weight
- Urinary glucose excretion
- Weight

Adding Metformin or Thiazolidinediones to Insulin Therapy in T2DM vs Insulin Alone

Metformin + insulin
- No increase in risk of severe hypoglycemia
- No increased risk of nonsevere hypoglycemia
- Reduces A1C by 0.8%
- Reduces body weight by 1.7 kg
- Reduces insulin dose
- No increase in all-cause or cardiovascular mortality

Pioglitazone + insulin
- Slightly increased risk of any hypoglycemia (RR = 1.27, P = .06)
- Severe hypoglycemia infrequent
- Reduces A1C by 0.8%
- Increases body weight by 2.91 kg

Rosiglitazone + insulin
- Insulin + rosiglitazone is neither recommended nor approved

Adding DPP-4 Inhibitors to Insulin Therapy in T2DM Does Not Increase the Risk of Severe Hypoglycemia vs Insulin Alone

Nonsevere Hypoglycemia
- DPP-4I + INS vs Placebo + INS

Severe Hypoglycemia
- DPP-4I + INS vs Placebo + INS

Adding a DPP-4I to insulin reduces A1C ~ 0.6%-0.7% vs insulin alone
Scenes and Seminars on Hypoglycemia Management in Diabetes

Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Adding a SGLT2 Inhibitor to Insulin in T2DM
Does Not Greatly Increase the Risk of Hypoglycemia vs Insulin Alone

<table>
<thead>
<tr>
<th>Minor/Overall Hypoglycemia</th>
<th>Severe Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2</td>
<td>PBO</td>
</tr>
<tr>
<td>CANA 300 mg</td>
<td>DAPA 10 mg</td>
</tr>
<tr>
<td>EMPA 20 mg</td>
<td></td>
</tr>
<tr>
<td>46.6%</td>
<td>36.8%</td>
</tr>
<tr>
<td>40.3%</td>
<td>40.3%</td>
</tr>
<tr>
<td>24.0%</td>
<td>28.4%</td>
</tr>
<tr>
<td>20.5%</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

Clinical trials of 16-26 weeks duration.

http://www.accorddata.fda.gov/SingledriverOriginally

Adding a GLP-1 RA to Basal Insulin in T2DM May Cause Less Hypoglycemia Than Adding a Prandial Insulin

<table>
<thead>
<tr>
<th>Overall Hypoglycemia Rate, %</th>
<th>GLP-1 RA</th>
<th>Prandial insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIRA vs ASP + DEG</td>
<td>1.00</td>
<td>8.20</td>
</tr>
<tr>
<td>EXN BID vs LIS + GLAR</td>
<td>2.10</td>
<td>5.00</td>
</tr>
<tr>
<td>ALBI QW vs LIS + GLAR</td>
<td>0.90</td>
<td>2.30</td>
</tr>
</tbody>
</table>

Adding a GLP-1 RA reduced A1C by 0.04%-0.32% and body weight by 1.5-3.75 kg vs adding prandial insulin.

Potential Strategies to Reduce Glycemic Variability

**Strategies in T1DM**

- Adding pramintide
- Adding a GLP-1 RA
- Adding a DPP-4 inhibitor
- Adding a SGLT2 inhibitor
- Ultralong-acting basal insulin analogues

**Strategies in T2DM**

- Adding a DPP-4 inhibitor
- Adding a GLP-1 RA + metformin
- Adding a SGLT2 inhibitor

References

SCENES AND SEMINARS ON HYPOGLYCEMIA MANAGEMENT IN DIABETES

Recognizing Hypoglycemia From Blood Glucose Monitoring Records

Clinical Pearls

- Hypoglycemia affects patient safety: patients using insulin therapy are at highest risk, but several strategies are available to reduce this risk.
- Glycemic variability is associated with the risk of complications of diabetes, including a greater risk of mortality with hypoglycemia.
- Stepwise insulin initiation reduces the risk of hypoglycemia with insulin therapy in T2DM.
- Newer agents for T2DM—DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 RAs—may improve glycemic control with neutral to beneficial effects on hypoglycemia.

Case Study: Pam

Presentation

<table>
<thead>
<tr>
<th>History</th>
<th>Current Medications</th>
<th>Laboratory Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patient, aged 64 years</td>
<td>Metformin 1000 mg bid</td>
<td>In-office glucose *110 mg/dL</td>
</tr>
<tr>
<td>T2DM, 15 years</td>
<td>Pioglitazone 15 mg/d</td>
<td>A1C = 6.3%</td>
</tr>
<tr>
<td>Hypertension, 18 years</td>
<td>Basal insulin analogue 23 units at bedtime</td>
<td>BP: 135/85</td>
</tr>
<tr>
<td>Dyslipidemia, 14 years</td>
<td>ARB, CCB, HCTZ</td>
<td>Lipids: normal</td>
</tr>
<tr>
<td>Height: 5'6&quot;</td>
<td>Statin</td>
<td>eGFR = 58 mL/min</td>
</tr>
<tr>
<td>Weight: 172 lb</td>
<td></td>
<td>LFTs: normal</td>
</tr>
<tr>
<td>BMI: 27.8 kg/m²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the last 2 months, Pam has noticed that her morning glucose levels have been high, and go even higher after a low-carbohydrate breakfast.
- Pam has self-titrated her bedtime basal insulin dose from 18 units to 22 units, but her morning SMBG levels remain increased.
- She explains that she doesn’t like to bother her nurse with minor problems, which is why she hasn’t called about the dose adjustments.
- Upon questioning, she mentions that she feels unexpectedly tired when she gets up in the morning.

Pam’s Blood Glucose Monitoring Record

Pam wonders why more basal insulin isn’t reducing her blood glucose levels.
Recognizing Hypoglycemia From Blood Glucose Monitoring Records

LIVE QUESTION-AND-ANSWER SESSION
**Resoures**

**GENERIC DRUG NAMES AND ASSOCIATED BRANDS**

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Associated Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>albiglutide</td>
<td>Tanzeum</td>
</tr>
<tr>
<td>alogliptin</td>
<td>Nesina</td>
</tr>
<tr>
<td>allopurinol</td>
<td>Alopurin, Lopurin, Zyloprim</td>
</tr>
<tr>
<td>aspirin</td>
<td>8-Hour Bayer, Measurin; often combined with other analgesics</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>Invokana</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>Farxiga</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Januvia, Nesina, Onglyza, Tradjenta</td>
</tr>
<tr>
<td>empagliflozin</td>
<td>Jardiance</td>
</tr>
<tr>
<td>exenatide</td>
<td>Byetta, Bydureon</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Bydureon, Byetta, Tanzeum, Trulicity, Victoza</td>
</tr>
<tr>
<td>glinide</td>
<td>Prandin, Starlix</td>
</tr>
<tr>
<td>glyburide</td>
<td>Diabeta, Glynase, Micronase</td>
</tr>
<tr>
<td>insulin aspart</td>
<td>Novolog</td>
</tr>
<tr>
<td>insulin degludec</td>
<td>Investigational product in the United States; European brand name: Tresiba</td>
</tr>
<tr>
<td>insulin detemir</td>
<td>Leurmir</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>Lantus</td>
</tr>
<tr>
<td>insulin glulisine</td>
<td>Apidra</td>
</tr>
<tr>
<td>insulin lispro</td>
<td>Humalog</td>
</tr>
<tr>
<td>linagliptin</td>
<td>Tradjenta</td>
</tr>
<tr>
<td>liraglutide</td>
<td>Victoza</td>
</tr>
<tr>
<td>metformin</td>
<td>Glucophage</td>
</tr>
<tr>
<td>NPH insulin</td>
<td>Humulin N, Novolin N, ReliOn N</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td>rosiglitazone</td>
<td>Avandia</td>
</tr>
<tr>
<td>saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>Farxiga, Invokana, Jardiance</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>sulfonylurea</td>
<td>Glynase, Diabeta, Amaryl</td>
</tr>
<tr>
<td>TZD</td>
<td>Actos, Avandia</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>Proloprim; often combined with sulfamethoxazole</td>
</tr>
<tr>
<td>warfarin</td>
<td>Athrombin, Coumadin, Jantoven, Panwarfin</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4B</td>
<td>Basal Insulin Glargine + Exenatide BID vs Basal Insulin Glargine + Bolus Insulin Lispro Study (NCT00960661)</td>
</tr>
<tr>
<td>4T</td>
<td>Treating to Target in Type 2 Diabetes Trial (NCT00184600)</td>
</tr>
<tr>
<td>A1C</td>
<td>Glycated Hemoglobin</td>
</tr>
<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>ADT</td>
<td>Adjust-to-Target, Adjust to Target in Type 2 Diabetes Study (NCT00135057)</td>
</tr>
<tr>
<td>ALBI QW</td>
<td>Albiglutide Once-Weekly</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin-Receptor Blocker</td>
</tr>
<tr>
<td>ASP</td>
<td>Insulin Aspart</td>
</tr>
<tr>
<td>AT.LANTUS</td>
<td>A Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Subjects With Uncontrolled Blood Sugar (NCT00390728)</td>
</tr>
<tr>
<td>AUTONOMY</td>
<td>Study of Insulin Lispro in Patients With Inadequately Controlled Type 2 Diabetes (NCT01215955)</td>
</tr>
<tr>
<td>BBT</td>
<td>Basal-bolus Therapy</td>
</tr>
<tr>
<td>BEGIN</td>
<td>Comparison of the Efficacy and Safety of Two Intensification Strategies in Subjects With Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin (NCT01388361)</td>
</tr>
<tr>
<td>BG</td>
<td>Blood Glucose</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>CANA</td>
<td>Canagliflozin</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium Channel Blocker</td>
</tr>
<tr>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
</tr>
<tr>
<td>CR</td>
<td>Counterregulatory</td>
</tr>
<tr>
<td>CSII</td>
<td>Continuous Subcutaneous Insulin Infusion</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>DAPA, dapagliflozin</td>
<td></td>
</tr>
<tr>
<td>DEG, insulin degludec</td>
<td></td>
</tr>
<tr>
<td>DET, insulin detemir</td>
<td></td>
</tr>
<tr>
<td>DPP-4 i, dipeptidyl peptidase-4 inhibitor</td>
<td></td>
</tr>
<tr>
<td>DURABLE, Evaluating the Durability of Starter Insulin Regimens With Type 2 Diabetes (IOOV) (NCT00279201)</td>
<td></td>
</tr>
<tr>
<td>EASD, European Association for the Study of Diabetes</td>
<td></td>
</tr>
<tr>
<td>eGFR, estimated glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td>EMPA, empagliflozin</td>
<td></td>
</tr>
<tr>
<td>EPY, events per year</td>
<td></td>
</tr>
<tr>
<td>EXN BID, exenatide twice-daily</td>
<td></td>
</tr>
<tr>
<td>FBG, fasting blood glucose</td>
<td></td>
</tr>
<tr>
<td>FPG, fasting plasma glucose</td>
<td></td>
</tr>
<tr>
<td>FullSTEP, Efficacy and Safety of Basal-bolus Therapy, Comparing Stepwise Addition of Insulin Aspart Versus Complete Basal-bolus Regimen (NCT01165684)</td>
<td></td>
</tr>
<tr>
<td>GLAR, insulin glargine</td>
<td></td>
</tr>
<tr>
<td>GLP-1 RA, glucagon-like peptide-1 receptor agonist</td>
<td></td>
</tr>
<tr>
<td>GLU, insulin glulisine</td>
<td></td>
</tr>
<tr>
<td>Harmony 6, A Study to Determine the Safety and Efficacy of Albiglutide Administered in Combination With Insulin Glargine (NCT00976391)</td>
<td></td>
</tr>
<tr>
<td>HCP, healthcare provider</td>
<td></td>
</tr>
<tr>
<td>HCTZ, hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>INS, insulin</td>
<td></td>
</tr>
<tr>
<td>LFTs, liver function tests</td>
<td></td>
</tr>
<tr>
<td>LIRA, liraglutide</td>
<td></td>
</tr>
<tr>
<td>LIS, insulin lispro</td>
<td></td>
</tr>
<tr>
<td>NPH, neutral protamine Hagedorn</td>
<td></td>
</tr>
<tr>
<td>OPAL, Orals Plus Apidra and Lantus Study (NCT00272012)</td>
<td></td>
</tr>
<tr>
<td>OSIRIS, Opposing Step-by-step Insulin Reinforcement to Intensified Strategy (NCT00174642)</td>
<td></td>
</tr>
<tr>
<td>PBO, placebo</td>
<td></td>
</tr>
<tr>
<td>PPG, postprandial plasma glucose</td>
<td></td>
</tr>
<tr>
<td>PREDICTIVE 303, Comparison of Self Adjustment Versus Standard of Care Treatment in Subjects With Type 2 Diabetes (NCT00264901)</td>
<td></td>
</tr>
<tr>
<td>PREFER, Efficacy and Safety of Insulin Detemir in Combination With Insulin Aspart and Biphasic Insulin Aspart 30 in Type 2 Diabetes (NCT00605020)</td>
<td></td>
</tr>
<tr>
<td>QOL, quality of life</td>
<td></td>
</tr>
<tr>
<td>RR, relative risk</td>
<td></td>
</tr>
<tr>
<td>SD, standard deviation</td>
<td></td>
</tr>
<tr>
<td>SGLT2, sodium glucose cotransporter-2</td>
<td></td>
</tr>
<tr>
<td>SMBG, self-monitored blood glucose</td>
<td></td>
</tr>
<tr>
<td>START, Self-titration With Apidra to Reach Target (NCT01013571)</td>
<td></td>
</tr>
<tr>
<td>STeP, Structured Testing Program (NCT00674986)</td>
<td></td>
</tr>
<tr>
<td>STEPwise, Comparison of the Blood Sugar Lowering Effect and Safety of Two Insulin Treatments in Type 2 Diabetes (NCT00537303)</td>
<td></td>
</tr>
<tr>
<td>SU, sulfonylurea</td>
<td></td>
</tr>
<tr>
<td>T1DM, type 1 diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>T2DM, type 2 diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>TDD, total daily dose</td>
<td></td>
</tr>
<tr>
<td>TZDs, thiazolidinediones</td>
<td></td>
</tr>
</tbody>
</table>
## Basal Insulin Titration—Examples

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADA/EASD³</th>
<th>AACE²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>10 U/d or 0.2 U/kg</td>
<td>A1C &lt; 8%: 0.1-0.2 U/kg A1C &gt; 8%: 0.2-0.3 U/kg</td>
</tr>
<tr>
<td>Titration</td>
<td>2 U every 3 d to FBG 70-130 mg/dL</td>
<td>Titrate dose every 2-3 d Fixed regimen—add 2 U Adjustable regimen: FBG &gt; 180 mg/dL: add 4 U FBG 140-180 mg/dL: add 2 U FBG 110-139 mg/dL: add 1 U Hypoglycemia: reduce dose 10% to 40%, depending on BG level</td>
</tr>
<tr>
<td></td>
<td>Can increase by larger increments (eg, 4 U) if FBG &gt; 180 mg/dL</td>
<td>Hypoglycemia: reduce dose by the greater of 4 U or 10%</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia: reduce dose by the greater of 4 U or 10%</td>
<td></td>
</tr>
</tbody>
</table>

---

## Prandial Insulin Titration—Examples

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADA/EASD³</th>
<th>AACE²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>Test premeal BG; if value is above range, add insulin at previous meal Add ≈ 4 U</td>
<td>TDD: 0.3-0.5 U/kg 50% basal analogue 50% prandial analogue</td>
</tr>
<tr>
<td>Titration</td>
<td>2 U every 3 days</td>
<td>• If premeal BG &gt; 180 mg/dL, add 10% at next meal • If 2-h postmeal BG &gt; 180 mg/dL, add 10% at that meal Hypoglycemia: • If fasting AM, reduce basal • If nighttime, reduce basal and/or presupper or pre-evening snack insulin • If between meals, reduce previous premeal insulin</td>
</tr>
</tbody>
</table>

---
