Session 9: Integrating Insulin and New Therapies Into Type 2 Diabetes Management: Current Answers to Key Questions

Learning Objectives

- Incorporate emerging therapies, including the GLP-1 analogues and DPP-4 inhibitors, into several different treatment plans for patients with type 2 diabetes.
- Describe a therapeutic management program for initiating and intensifying insulin therapy according to current management guidelines.

Faculty

**Philip Levy, MD, MACE**
Clinical Professor of Medicine  
University of Arizona College of Medicine  
Phoenix  
Chairman, Section of Endocrinology and Metabolism  
Banner Good Samaritan Regional Medical Center  
Phoenix

Dr Levy graduated from the University of Pittsburgh School of Medicine, in Pennsylvania. He completed his internship, internal medicine residency, and fellowship in metabolism and endocrinology at Michael Reese Hospital and Medical Center in Chicago, Illinois. He was a research fellow in endocrinology at Guy’s Hospital Medical Center in London, England.

Dr Levy is board certified in internal medicine, metabolism, and endocrinology, and nuclear medicine. Dr Levy is a clinical professor of medicine at the University of Arizona College of Medicine and chairman of the Section of Endocrinology and Metabolism at Banner Good Samaritan Regional Medical Center in Phoenix, Arizona. He is a member of the American Association of Clinical Endocrinologists (AACE), the American College of Physicians, the Endocrine Society, the American Diabetes Association (ADA), and the American Thyroid Association. Dr Levy was honored at this year’s AACE meeting with a mastership of The American College of Endocrinology (MACE). He previously served on the boards of directors of the ADA and AACE and was also vice president, then president of the American College of Endocrinology (ACE) from 2002-2004.

**Lawrence S. Phillips, MD**
Professor of Medicine  
Division of Endocrinology  
Emory University School of Medicine  
Atlanta, Georgia

Dr Phillips was educated at Swarthmore College, Swarthmore Pennsylvania, and Harvard Medical School, Boston, Massachusetts, followed by residency at Rush University Medical Center, Chicago, Illinois, and fellowship training at Washington University School of Medicine, St Louis, Missouri. He is board certified in internal medicine and endocrinology and metabolism, is listed as one of the Best Doctors in America, and has been a professor of medicine at Emory University, Atlanta, Georgia, for 25 years. At Emory, he has been director of the Division of Endocrinology and Metabolism, program director of the General Clinical Research Center, and medical director of the Clinical Studies Center at the Atlanta VA Medical Center. He has been engaged in research, teaching, and the clinical practice of endocrinology for over 35 years, and has published over 150 articles in peer-reviewed journals. He has received funding from the National Institutes of Health for research in physiology, molecular biology, and improving diabetes management.

**Robert E. Rakel, MD**
Professor  
Department of Family and Community Medicine  
Baylor College of Medicine  
Houston, Texas

Dr Rakel graduated from the University of Cincinnati College of Medicine, in Ohio. After residencies in internal medicine and general practice, Dr Rakel was in private practice as a family physician in Newport Beach, California. In
1969, he was appointed the first chairman of family medicine at the University of California, Irvine, College of Medicine. In 1971, he was selected to develop the Department of Family Practice at the University of Iowa, Iowa City, and served as the head of that department for 15 years. From 1985 to 1997, he served as associate dean for academic and clinical affairs and Richard M. Kleberg Senior Professor and Chairman, Department of Family Medicine at Baylor College of Medicine, Houston, Texas. He is currently a professor in the Department of Family and Community Medicine, Baylor College of Medicine.

Dr Rakel has written and/or edited more than 50 books. He is editor of the *Textbook of Family Medicine* (7th edition, 2007), and has been editor of *Conn’s Current Therapy* since Dr Conn’s death in 1983.

**Faculty Financial Disclosure Statements**
The presenting faculty report the following:

Dr Levy receives grants for research from Amylin Pharmaceuticals, Inc.; Daiichi Sankyo, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; and sanofi-aventis U.S. He is on speakers bureaus and receives honoraria from Amylin Pharmaceuticals, Inc.; Eli Lilly and Company; GlaxoSmithKline; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Novo Nordisk Inc.; Pfizer Inc.; sanofi-aventis U.S.; and Takeda Pharmaceuticals North America, Inc.

Dr Phillips does research, consults, speaks for, and/or serves on advisory panels for Amylin Pharmaceuticals, Inc.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Novo Nordisk Inc.; and Pfizer Inc. He receives honoraria, fees, and/or financial support for research from these companies.

Dr Rakel receives honoraria from Novo Nordisk.

**Education Partner Financial Disclosure Statement**
The content collaborators at DesignWrite have nothing to disclose.

**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>acarbose</td>
<td>Precose</td>
<td>isophane insulin</td>
<td>various</td>
</tr>
<tr>
<td>aspirin</td>
<td>various</td>
<td>metformin</td>
<td>various</td>
</tr>
<tr>
<td>colesevelam</td>
<td>Welchol</td>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>exenatide</td>
<td>Byetta</td>
<td>pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td>glipizide</td>
<td>Glucotrol</td>
<td>ramipril</td>
<td>Altace</td>
</tr>
<tr>
<td>hydrochlorothiazide</td>
<td>various</td>
<td>repaglinide</td>
<td>Prandin</td>
</tr>
<tr>
<td>insulin aspart</td>
<td>NovoLog</td>
<td>rosvastatin</td>
<td>Crestor</td>
</tr>
<tr>
<td>insulin aspart 70/30</td>
<td>NovoLog Mix 70/30</td>
<td>simvastatin</td>
<td>Zocor</td>
</tr>
<tr>
<td>insulin detemir</td>
<td>Levemir</td>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>insulin glargine</td>
<td>Lantus</td>
<td>Humalog</td>
<td></td>
</tr>
<tr>
<td>insulin glulisine</td>
<td>Apidra</td>
<td>Humalog mix 75/25</td>
<td></td>
</tr>
<tr>
<td>insulin lispro</td>
<td>Humalog</td>
<td>Humalog mix 75/25</td>
<td></td>
</tr>
<tr>
<td>insulin lispro 75/25</td>
<td></td>
<td>Humulin</td>
<td></td>
</tr>
<tr>
<td>insulin recombinant human</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigational</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>liraglutide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>vildagliptin</td>
<td></td>
</tr>
</tbody>
</table>

**Suggested Reading List**


Integrating Insulin and New Therapies into Type 2 Diabetes Management: Current Answers to Key Questions

Learning Objectives

- Incorporate emerging therapies, including the GLP-1 analogs and DPP-4 inhibitors, into several different treatment plans for patients with type 2 diabetes
- Describe a therapeutic management program for initiating and intensifying insulin therapy according to current management guidelines

Integrating Insulin and New Therapies into Type 2 Diabetes Management

AGENDA

12:30 – 12:50 PM Overcoming Clinical Inertia in the Treatment of Type 2 Diabetes Lawrence S. Phillips, MD

12:50 – 1:10 PM Case Study 1: Changing Therapy for a Patient with Type 2 Diabetes Currently Treated with OADs Philip Levy, MD

1:10 – 1:30 PM Case Study 2: Initiating Insulin Therapy for a Patient with Type 2 Diabetes Robert E. Rakel, MD

1:30 – 1:45 PM Questions and Answers Faculty

You Have Responsibility for Your Patients’ Outcomes

- Most patients are adherent
  - Keeping appointments
  - Taking medications
  - … can’t expect weight loss …
- It’s up to you to
  - Control their diabetes
  - Minimize their associated risks
  - Find their complications early

Diabetes Outcomes Are Hard to Improve

Healthy People 2000 Goals for Americans

- Increase the years of healthy life
- Reduce health disparities
- Achieve access to preventive services

- Heart disease deaths ↓ National goal met
- Cancer deaths ↓ National goal met
- Diabetes deaths No improvement
- Diabetes years of healthy life Worse

Percentages of adults with type 2 diabetes achieving goals for CVD risk factors

BP = blood pressure; CVD = cardiovascular disease.

Most Patients With Type 2 Diabetes Do Not Achieve Risk Factor Control

Vascular Disease Risk Factors

- HbA1c <7.0%
- BP <130/80 mm Hg
- Total Cholesterol <200 mg/dL

All 3 Factors at Goal

NHANES III 1988-1994 (n = 1204)
NHANES 1999-2000 (n = 370)
NHANES 1999-2002
NHANES 2003-2004

Basis for Diabetes “Epidemic”

- Diabetes epidemic fueled by insulin resistance
  - Aging, obesity, sedentary activity
- High blood glucose is due to lack of insulin
  - Genetic risk (↑ in racial/ethnic minorities)
- Most patients have a dual defect
  - ↓ Insulin action and ↓ insulin secretion

Concept #1: In people with insulin resistance, diabetes develops if β-cell function is inadequate to meet the challenge

Concept #2: To improve glucose levels, we must improve insulin action, and/or raise insulin levels

Inadequate Diabetes Control – Patient “Noncompliance” vs Provider “Clinical Inertia”?

- Patient “noncompliance”: patients who are obese but do not lose weight or exercise (similar to most Americans)
- Provider “clinical inertia”: failure to intensify therapy for high glucose

Glucose Levels May Not Improve in Obese Diabetes Patients Who Lose 20 lb

RPG = random plasma glucose.

Diabetes Rx Often Not Intensified Despite High Glucose Levels

Therapy intensification (%)

- A1C > 7%
- FPG > 140
- A1C > 8%
- FPG > 170
- A1C > 9%
- FPG > 200


Initiation of Diabetes Rx
Kaiser Permanente 1999-2002

A1C improves, but few patients reach goal

Mean A1C

- Insulin
- Thiazolidinedione
- Metformin
- Sulfonylurea

Initiation of Diabetes Rx – Kaiser
3- to 12-Month A1C < 7%

Goal reached more often when Rx started early

Preinitiation Hemoglobin A1C

Responsibility of Patient Versus Provider

- “Health survival skills” for the patient include keeping appointments, taking Rx, exercise, diet, glucose monitoring, smoking cessation
- “Control” of BP, lipids, glucose, and use of aspirin depends largely on the provider
- Glucose triggers: A1C > 6.5%, office BG > 150 mg/dL or SMBG >100 premeal, >140 2h postmeal
- IF GLUCOSE IS > GOAL, DO SOMETHING – DO NOT GIVE IN TO “CLINICAL INERTIA”

A1C Can Be Improved by Interventions that Decrease Clinical Inertia

A1C (%) Med Clinic n = 2,062
7.4
7.6
7.8
8.0
8.2
8.4

7/99-12/99
1/00-6/00
7/00-12/00
1/01-6/01
7/01-12/01
1/02-6/02
7/02-12/02

Other prim care n = 1,519

Strategies for Clinicians to Avoid Clinical Inertia in T2DM Management

- Learn:
  - Benefits/(costs, side effects) of treating to target
  - Need to structure practice to aid management of disorders for which resolution of symptoms is not sufficient to guide care
- Strategies that can help:
  - Use reminders, get feedback on your performance
  - Use flow sheets as a routine – to follow test results, monitor therapies, and prompt action to achieve therapeutic goals

Earlier, More Aggressive Intervention Should Help Keep Glucose at Goal

Published Conceptual Approach

A1C (%) of patients

Mean A1C of patients

Conservative
Proactive

The Most Clinical Inertia in Diabetes Management is in Starting Insulin

- Problem:
  - Patients are reluctant to start insulin injections
  - Providers are reluctant to start pts on insulin
- This is “psychological insulin resistance”
- Solution:
  - Take the path of least resistance
  - Begin insulin Rx with basal insulin once a day
  - Use long-acting analog insulin in the evening
  - convenient for pts, low risk of hypoglycemia
Pharmacokinetics (in Type 1 DM Patients): Detemir vs Glargine

- Use both bid*
- Glargine: breakfast - supper
- Detemir: breakfast - bedtime

*Insulin glargine is not indicated for twice daily use.


6-Week Adjustment of Insulin Works; Weekly Phone Titration is Better

- Glargine adjusted q 6 weeks vs weekly
- A1C fell 1.3% 6 wk vs 1.5% weekly (P < .01)
- Only slightly more patients with A1C < 7% with point of care A1C vs standard lab (41% vs 36%, P < .0001)
- Conclusion: use algorithm


Titration Algorithm from the Canadian INSIGHT trial

- Begin long-acting insulin as 10 units every evening
- Measure fingerstick glucose every morning
- If the glucose is over 120 mg/dL, increase insulin dosage every day by adding 1 more unit of insulin
- Contact health-care provider for further instructions when morning fingerstick glucose levels fall below 120 mg/dL
- The eventual goal is to have morning fingerstick glucose no more than 100 mg/dL


Psychological Insulin Resistance

1. Lack of knowledge
2. Cultural taboos and family beliefs
3. Fear of needles or injection pain
4. Fear of hypoglycemia
5. Fear of weight gain
6. Inconvenience
7. Diabetes seen as worse or more serious
8. Personal failure
9. Insulin causes complications
10. Insulin will take over my life: constant demands and decision-making

Peragallo-Dittko V. Diabetes Educ. 2007;33(Suppl 3):60-5S.

Overcoming “Psychological Insulin Resistance”

- Discuss real risk of hypoglycemia (low)
- Address cultural taboos and family beliefs
- Fear of weight gain
  - Changes in food intake, exercise can minimize risk
- Refer patients starting insulin therapy
  - Experts in management: CDEs, dieticians, pharmacists
- Consider group education
  - Small-group instruction on insulin administration


Overcoming “Psychological Insulin Resistance” (cont.)

- Frame message properly (don’t “blame” the pt)
- Work to overcome needle phobia
  - Show fine needles, pens, devices that hide needles
  - Consider referral to behavioral therapy (“desensitization”)
- Convenience
  - Use available pens or dosers
- Begin therapy with a simple regimen
  - Detemir or glargine pen used in the evening – glargine at supper or detemir at bedtime

Summary

- Development of diabetes is a beta-cell problem
  - Management should aim at normal glucose to limit the work the beta cells must do
- Much of the problem is clinical inertia – we do not start and intensify insulin as we should
- Strategies to overcome "resistance to insulin" can help our patients to accept this therapy
- We need to use insulin early and aggressively

Case Study 1: Changing Therapy for a Patient with Type 2 Diabetes Currently Treated with OADs

Philip Levy, MD
Clinical Professor of Medicine
University of Arizona College of Medicine
Phoenix, Arizona

Case Study 1

- **Current history**
  - 51-year-old man diagnosed with type 2 diabetes 2 years ago
  - Dyslipidemia for at least one year
  - Does not exercise on a regular basis
- **Medications**
  - Glipizide 15 mg qd (every day) for 1 year
  - Metformin 1000 mg bid (twice a day) for 2 years
  - Rosuvastatin 10 mg for 1 year

- **Physical examination**
  - 5'10", 230 lbs, BMI = 33 kg/m²; BP = 130/80 mm Hg
- **Relevant laboratory findings**
  - A1C – 7.9%
  - FPG – 150 mg/dL; PPG – 240 mg/dL (based on self-monitored blood glucose [SMBG] readings)
  - Total cholesterol – 182 mg/dL
  - LDL-C – 92 mg/dL
  - HDL-C – 48 mg/dL
  - Triglycerides – 208 mg/dL

Treatment Options for Patients With Type 2 Diabetes on OADs

- **OADs from a different class**
  - TZDs, biguanides, bile acid sequestrants, sulfonylureas, glinides, α-glucosidase inhibitors, and DPP-4 inhibitors
- **GLP-1 analogs**
- **Insulin**

Incretin Hormones

- **INCRETIN** = INtestinal seCRETion of INSulin
- Secreted by the intestine in response to food intake
- Enhance insulin secretion in a glucose-dependent manner
- Include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino-mimetic polypeptide (GIP)
Actions of the Incretin Hormone
Glucagon-like Peptide-1 (GLP-1)

GLP-1 acts directly on the pancreas, heart, stomach, and brain, whereas actions on liver and muscle are indirect.

**Heart:**
- ↑ Cardioprotection
- ↑ Cardiac output

**Brain or CNS:**
- ↑ Neuroprotection
- ↓ Appetite

**Pancreatic islets:**
- ↑ Insulin biosynthesis
- ↑ β cell proliferation
- ↓ β cell apoptosis

**Gastrointestinal tract:**
- Stomach – ↓ Gastric emptying

**Periphery (liver, muscle, fat):**
- ↓ Glucose production
- ↑ Insulin secretion
- ↓ Glucagon secretion

---

**Case Study 1**

- **Treatment**
  - Initiated on 5 mcg bid of a GLP-1 analog (Exenatide) – dose was titrated up to 10 mcg bid after the first month of treatment
  - Metformin and glipizide were both continued for optimal glycemic control

- **Results after 3 months**
  - A1C – 7.1%
  - FPG – 110 mg/dL; PPG – 180 mg/dL

**Case Study 1: Key Questions**

1. How do I incorporate new therapeutics into current clinical practice?
2. When should I implement changes in therapy?
3. What are some strategies for promoting patient education and self-care?

**Question 1: How do I incorporate new therapeutics into current clinical practice?**

- Analog preparations preferred; 2 prandial insulin can be added to any therapeutic intervention at any time to address persistent postprandial hyperglycemia; 3 a recent report (NEJM; 6/14/07) suggests a possible link of rosiglitazone to cardiovascular events that requires further evaluation; 4 cannot be used in NYHA CHF Class 3 or 4; 5 According to the FDA, rosiglitazone not recommended with insulin.

---

**Using Newer Glucose-Lowering Treatments in Combination Therapy**

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Generic Name</th>
<th>Recommended Initial Dosing</th>
<th>Indicated for Combination With</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 analogs</td>
<td>Exenatide</td>
<td>5 mcg bid</td>
<td>* Met + SU + Met + T2D</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Not currently available in the US</td>
<td></td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Sitagliptin</td>
<td>50 mcg qd</td>
<td>* Met + T2D</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td>Not currently available in the US</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Acarbose, Miglitol</td>
<td>25 mg bid at each meal</td>
<td>* Met + SU</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Pramlintide</td>
<td>60 mg (50% reduction of preprandial insulin)</td>
<td>* Met + SU</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam</td>
<td>6 tablets qd or 3 tablets bid (1 tablet = 625 mg)</td>
<td>* Met + SU</td>
</tr>
</tbody>
</table>

*Please see package inserts.*

---

**Change in Glycemic Parameters and Weight With Incretin Mimetics**

<table>
<thead>
<tr>
<th>GLP-1 analogs</th>
<th>Exenatide</th>
<th>Exenatide</th>
<th>Exenatide</th>
<th>Exenatide</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>–0.8*</td>
<td>–0.9*</td>
<td>–1.8*</td>
<td>–1.6*</td>
<td>–1.45*</td>
</tr>
<tr>
<td>≤7.0%</td>
<td>46.0</td>
<td>41.0</td>
<td>34.0</td>
<td>62.0</td>
<td>46.0</td>
</tr>
<tr>
<td>Change in weight (kg)</td>
<td>–2.8*</td>
<td>–1.8*</td>
<td>–1.8*</td>
<td>–1.5*</td>
<td>–2.991*</td>
</tr>
</tbody>
</table>

*These are different trials; juxtaposition for summary purposes and not meant to imply comparable patient groups. Liraglutide is currently in phase 3 clinical trials. Met = metformin; sulf = sulfonylurea; T2D = thiazolidinedione. All conclusions reviewed with Dr. Louis C. Matzkin and Dr. Scott H. Lipsett.*

---

**Change in A1C (%)**

- Exenatide + Met: –0.8*
- Exenatide + Sulfonylurea: –0.9*
- Exenatide + T2D: –1.8*
- Liraglutide: –1.45*
Using Newer Glucose-Lowering Treatments in Combination Therapy

- Incretin mimetics are indicated when combinations of OADs are not providing optimal glycemic control (when A1C levels are between 6.5% and 8.5%)
- DPP-4 inhibitors are useful for lowering postprandial glucose levels
- Pramlintide can be used in combination with insulin to control postprandial glucose


Question 2: When Should I Implement Changes in Therapy?

- Timing for various treatment options in the natural history of type 2 diabetes is critical
- 3 months should be the maximum duration for trials of therapy when A1C goals are not reached (unless there are known confounding issues that may be interfering with efficacy of therapy)1,2


OADs Often Fail to Maintain Control

- UKPDS data
  - 50% of patients after 3 years and 75% of patients after 9 years will need more than one oral agent
  - ~50% of patients in the UKPDS needed insulin to sustain glycemic control within 6 years after diagnosis3

Treatment in the UKPDS included diet, sulfonylurea, metformin, and insulin. Escalation of therapy occurred when FPG levels were above 15 mmol/L (conventional) or 6 mmol/L (intensive). Trend test for the difference in A1C between conventional and intensive treatment was significant (p < 0.0001). "UKPDS Study Group. Lancet. 1998;352:837-53 (reprinted with permission).

A1C Over Time in the UKPDS3

- Step 1: Lifestyle interventions and metformin
- Step 2: Additional medications
  - Insulin (for patients with A1C > 8.5)
  - Sulfonylurea
  - Incretin-based therapies (incretin mimetics, DPP-4 inhibitors)
  - TZD
  - Colesevelam
  - a-glucosidase inhibitors
- Step 3: Further adjustments
  - Insulin therapy (initiate or intensify)

Recommended Progression of Therapy

- Associated with increased risk of fluid retention, CHF, and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of MI.


Question 3: What are some strategies for promoting patient education and self-care?

- Involving interdisciplinary health care teams
- Using self-monitored blood glucose (SMBG)

Interdisciplinary Health Care Team

- Primary care physician
- Endocrinologist (diabetes clinic)
- Nurse practitioner
- Diabetes educator
- Nutritionist
- Pharmacist
Role of Self-Monitored Blood Glucose in Glycemic Control

- SMBG should be recommended as part of diabetes management because it provides:
  - Real-time blood glucose concentrations
  - Ability to assess pre- and postprandial hyperglycemia
  - Improved safety through detection of hypoglycemia
  - Possibility of timely therapeutic adjustments
- Meta-analyses support the benefit of SMBG in insulin-treated and non-insulin-treated patients

Case Study 2: Initiating Insulin Therapy for a Patient with Type 2 Diabetes

Robert E. Rakel, MD
Professor
Baylor College of Medicine
Houston, TX

Case Study 2

- Current history
  - 62-year-old woman diagnosed with type 2 diabetes 8 years ago
  - Has comorbidities of dyslipidemia and hypertension
  - Nonsmoker; walks 3 times/week (20 min/session)
- Medications
  - Metformin 1000 mg bid
  - Glipizide 5 mg qd
  - Pioglitazone 30 mg qd
  - Simvastatin 40 mg
  - Ramipril 10 mg
  - Hydrochlorothiazide 25 mg
  - Aspirin 81 mg

Case Study 2

- Physical characteristics
  - 5’4”, 150 lbs, BMI = 26 kg/m²; BP = 134/84 mm Hg
- Relevant findings
  - A1C – 8.5%
  - FPG – 180 mg/dL; PPG – 245 mg/dL (based on SMBG readings)
  - Total cholesterol – 184 mg/dL
  - LDL-C – 99 mg/dL
  - HDL-C – 41 mg/dL
  - Triglycerides – 220 mg/dL

Onset, Peak, and Duration of Action of Insulin Preparations

- Short-acting
  - Regular
  - Lispro, aspart, glulisine
- Intermediate-acting
  - NPH
- Long-acting
  - Detemir, glargine

While multiple treatment options exist for this patient, addition of insulin therapy provides the most effective lowering of A1C.
Insulin Analogs Versus Human Insulin

**Advantages**
- Mealtime convenience and flexibility with rapid-acting analogs
- Improved postprandial glycemic control with rapid-acting and premixed insulin analogs
- Less intrapatient variability with long-acting insulin analogs; also, similar glycemic control with less nocturnal hypoglycemia

**Disadvantages**
- Long-term safety of newer insulin analogs is not known
- For some patients without health insurance, the cost of insulin analogs may be a barrier

---

Long-Acting Insulin Analogs (Detemir, Glargine)

- Mimic physiologic basal insulin secretion; no distinct peak of action
- Less intrapatient variability in absorption compared with NPH insulin
- Decreased weight gain compared with NPH insulin
- Equivalent glycemic control with less risk of hypoglycemia compared to NPH insulin, particularly less nocturnal hypoglycemia
- One daily dose may be sufficient owing to longer (up to 24 hours) duration of action

---

Clinical Efficacy of Long-acting Insulin Analogs Added to OADs

**Insulin detemir**
- Mean FPG: 8.5, 7.2
- A1C %: 8.5, 7.2

**Insulin glargine**
- Mean FPG: 8.7, 7.2
- A1C %: 8.7, 7.2

---

Self-titration Algorithms

- Results from clinical trials using self-titration result in comparable or better glycemic control
- PREDICTIVE 3-0-3 algorithm
  - Increase by 3 U if > 110 mg/dL (>6.1 mmol/L)
  - No change if 80–110 mg/dL (4.4–6.1 mmol/L)
  - Reduce by 3 U if <80 mg/dL (<4.4 mmol/L)

---

Clinical Efficacy of Premixed Insulin Versus Long-acting Insulin Analogs

**Biphasic Insulin Aspart**
- Mean FPG: 9.7, 6.9
  - *P* < .01 vs glargine.

**Insulin Glargine**
- Mean FPG: 9.8, 7.4

---
### Insulin Dose Titration

<table>
<thead>
<tr>
<th>FPG Values (3-7 days)</th>
<th>Dosage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80 mg/dL</td>
<td>-2 units</td>
</tr>
<tr>
<td>80-109 mg/dL</td>
<td>No change</td>
</tr>
<tr>
<td>110-139 mg/dL</td>
<td>+2 units</td>
</tr>
<tr>
<td>140-179 mg/dL</td>
<td>+4 units</td>
</tr>
<tr>
<td>≥ 180 mg/dL</td>
<td>+6 units</td>
</tr>
</tbody>
</table>

Adjust prebreakfast dose based on presupper/evening FPG value.
Adjust presupper (premixed)/bedtime (basal) dose based on prebreakfast/morning FPG value.
DO NOT increase dose if hypoglycemia (<70 mg/dL) or symptoms are present.

FPG = fasting plasma glucose.

### Case Study 2: Treatment

- **Treatment**
  - Initiated on 10 U of a long-acting insulin analog (insulin detemir or glargine) given at bedtime and then titrated accordingly.
  - Continued on metformin (1000 mg twice a day) and pioglitazone (30 mg).
  - Discontinued glipizide (5 mg once a day) due to occurrence of hypoglycemia.

- **Results after 3 months**
  - A1C – 7.0%
  - FPG – 100 mg/dL; PPG – 175 mg/dL

### Case Study 2: Key Questions

1. How do I choose which type of insulin is appropriate for my patients?
2. How can weight gain typically associated with insulin therapy be minimized?
3. When and how should you intensify insulin therapy?

### Important Factors for Determining Use of Basal Insulin

- Patient preference and lifestyle considerations
  - Wants to maintain a more flexible schedule
  - Fears the potential complexities of insulin therapy
  - Dislikes the idea of injecting insulin, but initially only needs one daily injection if starting with a long-acting insulin analog (in most cases)
  - Prefers to maintain treatment with various oral agents when initiating insulin therapy

### Alternative Methods of Insulin Delivery

| Insulin Pens | Insulin Pumps |

---

Question 2: How can weight gain typically associated with insulin therapy be minimized?

- Long-term educational interventions that promote lifestyle changes
  - Meal modifications (ie, new preparation methods and portion size)
  - Increased physical activity
- Selection of therapy to limit weight gain
  - Some insulin analogs demonstrate less weight gain
  - Combining insulin with agents with beneficial or weight-neutral effects

Antihyperglycemic Agents Associated With Beneficial Weight Effects or Minimal Weight Gain

- Pramlintide
- GLP-1 analogs
- Metformin
- Insulin detemir
- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- Colesevelam

Emerging Diabetes Treatments Showing Body Weight Change From Baseline

- GLP-1 agonists
- Weight change (kg)
- HbA1c change (%)

Insulin Detemir: Changes in Weight by Baseline BMI

- Numbers above each bar show the number of patients within that category of treatment.

Question 3: When and how should you intensify insulin therapy?

- Severe insulin deficiency generally requires basal and prandial insulin replacement
  - Therapy should be initiated or intensified in patients not at goal (ADA: A1C < 7%; AACE: A1C ≤ 6.5%) on optimal doses

Both FPG and PPG Contribute to Elevated A1C in Patients With Type 2 Diabetes

- FPG = fasting plasma glucose
- PPG = postprandial plasma glucose

Strategies for Intensification

- Patients on basal insulin
  - Add rapid-acting insulin at one or more meals (usually the largest meal first)
  - Switch to a premixed insulin formulation
  - Switch to insulin pump therapy
- Patients on premixed insulin
  - Add a second or third dose (usually at breakfast or lunch)
  - Switch to basal-bolus therapy with long- and rapid-acting analogs
  - Switch to insulin pump therapy

Advancing Insulin Therapy in Patients Treated With Glargine Plus Oral Agents

- 374 patients were randomized to premixed therapy (lispro mix 50/50) or basal/bolus therapy (glargine plus mealtime lispro)
  - A1C at baseline:
    - 8.9% (basal-bolus)
    - 8.8% (premixed)
  - A1C at end point:
    - 6.78% (basal-bolus) vs 6.95% (premixed); P = .021

The 1–2–3 Study: Achievement of A1C Targets with Insulin Aspart 70/30

Data from completer population (n = 74); QD = once daily before dinner; BID = twice daily before breakfast and dinner; TID = thrice daily before breakfast, lunch, and dinner.

Conclusions

- Newer treatment options may enhance glycemic control while minimizing weight gain or promoting weight loss
- Insulin therapy should be
  - Tailored to the needs of the individual
  - Intensified when patients are not at goal on optimal doses of their current regimen
- Both basal and prandial insulin therapies are usually required with severe insulin deficiency