The Future of Basal Insulin

Improving Patient Outcomes by Addressing Unmet Needs

Dolores Gomez, MD

Expert Panel

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Expert Panel Disclosures

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Learning Objectives

1. Recognize patients who should receive basal insulin.
2. Employ strategies to overcome barriers that inhibit initiation of insulin.
3. Identify gaps in care for patients with type 2 diabetes who are being treated with basal insulin.
4. Differentiate between traditional basal insulin formulations and newly-approved/developmental formulations.
5. Integrate basal insulin into a patient-centered type 2 diabetes management plan

The Impact of Type 2 Diabetes

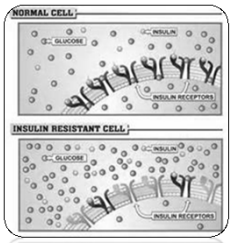
The Diabetes Epidemic

- ~29 million individuals in the US have diabetes (8.1 million are undiagnosed).[1]
- 7th leading cause of death in the US[1]
- In 2012, diabetes cost ~$245 billion in the US (> $1,000 per American).[2,3]
- An estimated 242,000 new cases per year in the US in next 20 years.[4]

Sources: [1]CDC. National diabetes statistics report, 2014; [2]American Diabetes Association. *Diabetes Care* 2013;36:1033-46; [3]Dall TM, et al. *Diabetes Care* 2014;37:3172-79; [4]Guariguata L, et al. *Diabetes Res Clin Pract* 2014;103:137-49.

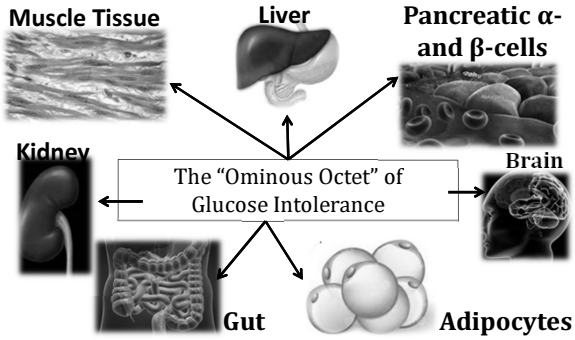
Type 2 Diabetes

- Insulin resistance in the muscles, liver, and adipose tissue
- Progressive decline in pancreatic β-cell function
- Uncontrolled hyperglycemia



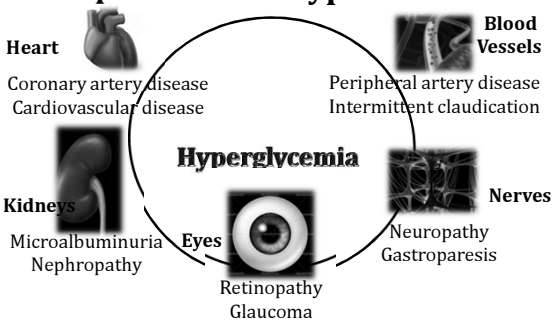
Source: ADA. *Diabetes Care.* 2015;8(Suppl 1):S8-S16.

Type 2 Diabetes Impacts Multiple Organs



Source: DeFronzo RA. *Diabetes* 2009;58:773-795.

Complications of Type 2 Diabetes



Source: ADA. *Diabetes Care.* 2010;33(Suppl 1):S11-S61.

Glycemic Control is Essential to Manage Disease

- Microvascular and macrovascular benefits are associated with glycemic control.[1-8]
- Target glucose levels should be individualized.
- Hypoglycemia should be avoided.

Sources: [1]UKPDS Group. *Lancet* 1998;352:837-53; [2]UKPDS Group. *Lancet* 1998;352:854-65; [3]Stratton IM, et al. *BMJ* 2000;321:405-12; [4]Diabetes Control and Complications Research Group. *N Engl J Med* 1993;329:977-86; [5]DCCT/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 2000;342:381-89; [6]Gaede P, et al. *N Engl J Med* 2003;348:383-93; [7]Lawson ML, et al. *Diabetes Care* 1999;22 (suppl 2):B35-B39; [8]Nathan DM, et al. *N Engl J Med* 2005;353:2643-53.

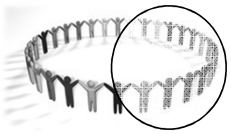
American Diabetes Association Glycemic Recommendations

A_{1c}	< 7.0%
Preprandial plasma glucose	80-130 mg/dL
Peak postprandial plasma glucose	< 180 mg/dL

Individualize based on age/life expectancy, duration of diabetes, comorbidities, known CVD or advanced microvascular complications, hypoglycemia unawareness, and patient preferences. More or less stringent goals may be appropriate for some patients.

Source: American Diabetes Association. *Diabetes Care* 2015;38(Suppl 1):S33-S40.

Reaching Glycemic Targets: Are We There Yet?



In 2010, 47% of American adults with diabetes had not achieved the ADA's management goal of A_{1c} < 7.0%.*

*Data from the National Health and Nutrition Examination Surveys (NHANES); 1988-2010.

Source: Stark Casagrande S, et.al. *Diabetes Care* 2013;36:2271-79.

Managing Diabetes

- Lifestyle interventions (diet, activity) for overweight/ obese individuals geared toward an initial loss of 5-10% of baseline body weight
- Cardiovascular risk management (e.g., hypertension, dyslipidemia, microalbuminuria)
- Normalizing blood glucose level
- Patient preferences and individualized goals

Pharmacotherapy for Type 2 Diabetes: An Overview

Diabetes Pharmacotherapy

- Oral antihyperglycemic agents
  - Sulfonylureas
  - Metformin
  - Thiazolidinediones
  - DPP-4 inhibitors
  - SGLT2 inhibitors
- Non-insulin injectable agents
  - GLP-1 agonists
- Insulin

Properties of Oral Antihyperglycemic Agents

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
TZDs	• PPAR-γ activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low
SGLT2 inhibitors	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	• ↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C	High

Source: Adapted from slide deck that accompanies Inzucchi SE, et.al. *Diabetes Care* 2015;38:140-49. Available at: http://care.diabetesjournals.org/content/38/1/140/suppl/DC2.

Considerations for Choosing Medication

- Efficacy for glycemic reduction
- Mechanism of action
- Side effects/contraindications
- Associated metabolic changes
- Patient preference/adherence
- Cost

Basic Principles

- Tailor regimen to patient's needs, as assessed through screening, interview, lab results
- Always include individualized regimen of lifestyle behaviors (diet, physical activity)
- Add pharmacotherapy as needed to control glycemia
- Treat to target.

Insulin can be initiated at any point in therapy.

Initiating Insulin Therapy for Patients with Type 2 Diabetes

Types of Insulin

- Short-acting (regular)
- Rapid-acting (e.g., glulisine, lispro, aspart)
- Intermediate-acting (neutral protamine Hagedorn [NPH])
- Basal (detemir, glargine)
- Pre-mixed formulations (rapid-acting + NPH)

Insulin types are characterized by onset, peak time, and duration of action.

Types of Insulin

	Short-acting	Rapid-acting	Intermediate-acting	Basal	Pre-mixed
Onset	30 min	15 min	2-4 hr	2-6 hr	5-15 min
Peak time	2-3 hr	1 hr	6-16 hr	None	Varies
Duration of Action	3-6 hr	2-4 hr	12-18 hr	24 hr	10-16 hr

Source: American Diabetes Association. Insulin basics. 2015. http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html.

Features of Commercial Insulins

- Manufactured in laboratory (biosynthetic human insulins or insulin analogs)
- Standard strength is 100 units/mL (U-100), although some U-300 and U-500 formulations are available
- Nearly all insulins are injectable, although an inhaled rapid-acting insulin was FDA-approved in 2014[1]

Source: [1]Tucker ME. *Medscape Medical News*. 2014. http://www.medscape.com/viewarticle/822957.

Insulin Side Effects

- Weight gain (generally 1-3 kg more than with other agents)[1]
- Hypoglycemia (characterized by dizziness, hunger, blurred vision, and tachycardia)[2]

Hypoglycemic episodes that diminish cerebral glucose supply can lead to confusion and potentially dangerous cognitive impairment.

Sources: [1]Garber AJ, Abrahamson MJ, Barzilay JI, et al. *Endocr Pract* 2013;19:327-36; [2]UK Hypoglycaemia Study Group. *Diabetologia* 2007;50:1140-47.

Overcoming Barriers to Insulin Use

Using Insulin Effectively: Are We There Yet?

Although insulin is an expedient tool to achieve glycemic control, numerous surveys indicate **suboptimal commitment** to prescribe or use insulin, even when clinically warranted.

Source: Edelman S, Pettus J. *Am J Med* 2014;127:S11-S16.

Physician-Based Barriers

- "Clinical inertia":[1]
  - Insulin seen as "last-resort" therapy
  - Lack of knowledge about insulin use
  - Concerns that patients will fail to adhere or be displeased
- Association with hypoglycemia[2]

Sources: [1]Peyrot M, et al. *Diabetes Care* 2005;28:2673-79; [2]Peyrot M, et.al. *Diabet Med* 2012;29:682-89.

Patient-Based Barriers

- Fear of injections
- Association with hypoglycemia/weight gain
- Uncertainty about titrating dose or coordinating injections with lifestyle
- Perception that insulin use signals deterioration of condition or failure of management
- Perception that insulin therapy is permanent once initiated

Source: Edelman S, Pettus J. *Am J Med* 2014;127:S11-S16.

Overcoming Barriers

- Communicate to individualize regimen
- Be flexible to patient's needs and concerns
- Explain objectively the progressive nature of type 2 diabetes and therapeutic options
- Contextualize insulin as an effective tool, not a failure of other interventions
- State practical benefits of insulin (glucose control, simplifying regimen, reducing number of medications and side effects, immediate results)

Sources: ADA. *Diabetes Care* 2015;38 (Suppl 1):S41-S48; Edelman S, Pettus J. *Am J Med* 2014;127:S11-S16.

Facilitating Insulin Use

- Demonstrate techniques for subcutaneous injection
- Provide algorithm for self-titrating insulin dose based on self-monitored blood glucose
- Connect patient with a Certified Diabetes Educator (CDE) when possible
- Educate family members and significant others about insulin use

Source: Edelman S, Pettus J. *Am J Med* 2014;127:S11-S16.

Basal Insulin: Indications, Formulations, and Use in Type 2 Diabetes Management

Basal Insulin Indications

- Three agents (detemir, glargine U-100 and U-300) are FDA-approved to improve glycemic control in children and adults with diabetes
- Not recommended for diabetic ketoacidosis
- FDA Pregnancy Category B (detemir) or C (glargine)

Source: Package inserts for detemir, glargine U-100, and glargine U-300.

Comparing Glargine U-100 and U-300

- U-300 and U-100 equally efficacious for controlling A_{1c} in:
  - Individuals who received $\geq$ 42 U/day of basal insulin plus mealtime insulin[1,2]
  - Individuals who received $\geq$ 42 U/day of basal insulin plus oral antihyperglycemic agents[3]
  - Insulin-naïve individuals[4]
- U-300 associated with less hypoglycemia than U-100 in these populations[1-4]

Sources: [1]Riddle MC, et al. *Diabetes Care* 2014;37:2755-62; [2]Riddle MC, et al. *Diabetes Obes Metab* 2015;Apr 2:Epub ahead of print; [3]Yki-Järvinen H, et al. *Diabetes Care* 2014;37:3235-43; [4]Bolli GB, et al. *Diabetes Obes Metab* 2015;17:386-94.

Investigational Basal Insulins

- Insulin degludec
  - Ultra-long-lasting insulin analog
  - Submitted to FDA; approval contingent on outcome of ongoing cardiovascular safety trial
- Peglyated lispro
  - Insulin lispro with a covalently-bound polyethylene glycol chain that alters distribution and reduces renal clearance
  - Currently in Phase III trials

Source: Package inserts for detemir, glargine U-100, and glargine U-300.

Basal Insulin: 2015 ADA/EASD Recommendations

- With metformin in dual therapy
- With metformin + TZD, DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 agonist (triple therapy)
- With mealtime insulin or GLP-1 agonist as initial therapy for blood glucose $\geq$ 300-350 mg/dL and/or $A_{1c} \geq$ 10-12%, esp. if symptomatic or if catabolic features present

Source: Inzucchi SE, et.al. *Diabetes Care* 2015;38:140-49.

Titrating Basal Insulin

- Individualize starting dose (suggest 10 U or 0.1-0.2 U/kg per day insulin-naïve patients)
- Take once daily (at same time each day)
- Adjust dose regularly (e.g., weekly) based on daily self-monitored blood glucose
- Reduce titration increment as FPG approaches target.

Source: ADA. *Diabetes Care* 2015;38 (Suppl 1):S41-S48.

Titrating Basal Insulin

If basal insulin is titrated to acceptable FPG, but A_{1c} remains above target, ADA recommends a "basal-bolus" regimen.*

Basal Insulin + Rapid-acting insulin (or GLP-1 agonist) before meals ⇨
- Flexible
- Covers mealtime glycemic variations

*Consider discontinuing SU, DPP-4, and/or GLP-1 agents when insulin regimen becomes more complex and costly.

Source: Inzucchi SE, et.al. *Diabetes Care* 2015;38:140-149.

Shared Decision-Making in Diabetes Management

- Personalized management plan
- Self-management education
- Adherence to treatment
- Appropriate follow-up and monitoring

The ADA/EASD recommendations support a shared decision-making approach that applies to primary care practices.

Source: Inzucchi SE, et al. *Diabetes Care* 2015;38:140-49.

Management Requires Active Patient Participation

- Maintain daily diet/ exercise diary
- Identify/avoid high-risk situations
- Reward success
- Set realistic goals

- Establish a self-management plan based on what the patient feels that he/she can achieve confidently

Online Resources

Organization	URL
American Diabetes Association	www.diabetes.org
American Academy of Family Physicians	www.aafp.org
American Association of Diabetes Educators	www.diabeteseducator.org
American Association of Clinical Endocrinologists	www.aace.com

Case Study

Hannah

Case Study: Hannah

- 61-year-old African-American with diabetes (BMI = 29 kg/m^2)
- Diagnosed with type 2 diabetes ten years ago
- Currently takes ACE inhibitor and statin
- Takes metformin, DPP-4 inhibitor, and sulfonylurea (all at maximum dose) regularly
- Cannot tolerate GLP-1 agonists

Case Study: Hannah

- Reports frequent urinary tract infections
- Her A_{1c} has increased incrementally for the previous year
- Has attended diabetes education classes but admits difficulty maintaining resolve with diet and exercise
- Reports to office regularly every 3 months

Case Study: Hannah

Hannah's laboratory workup values include:

- A_{1c}: 8.7% (was 7.5% one year ago)
- Blood pressure: 140/80 mm Hg
- eGFR: 64 mL/min/1.73 m^2
- No signs of volume depletion

Case Study: Hannah

1. According to ADA guidelines, which of the following is a reasonable A_{1c} goal for Hannah?

a) 5.8%
b) 6.0%
c) 6.5%
d) 7.0%
e) 8.0%

Case Study: Hannah

2. What should you do at this point to help Hannah achieve glycemic control?

a) Add a fourth oral agent
b) Initiate basal insulin and discontinue all oral medications
c) Add basal insulin to current regimen
d) Add mealtime insulin to current regimen
e) Initiate a premixed insulin formulation

Case Study: Hannah

3. How should you counsel Hannah at this point?

a) Help her locate a Certified Diabetes Educator (CDE) who can teach her about self-management and a dietitian to help promote healthy eating habits
b) Reiterate importance of maintaining a healthy lifestyle
c) Emphasize that insulin is now necessary to manage disease
d) Discuss importance of monitoring her blood glucose to optimize control and avoid hypoglycemia
e) All of the above.

Case Study: Hannah

4. When counseling Hannah about insulin, which of the following options is NOT advisable to discuss with her?

a) Tell her that insulin is necessary and should be considered sooner rather than later.
b) Stat that insulin is highly effective and will help her control her diabetes.
c) Reiterate that insulin is a last-stage intervention brought about by the failure of oral agents.
d) Help her locate a CDE and possibly a support group to help manage psychological adjustment to initiating insulin

Case Study: Hannah

5. You tell Hannah how to recognize symptoms of hypoglycemia and show her how to inject insulin at an initial dose of 0.1 U/kg. You instruct her to take the basal insulin in the morning and titrate as needed. Several days later, she reports feeling light-headed and says that she is experiencing hypoglycemic episodes in the afternoon. She states that her blood sugar, which is at a baseline of ~ 180 mg/dL, approaches 60 mg/dL in the afternoon. She currently takes oral agents in the morning. What would you suggest to do next?

Case Study: Hannah

5. (continued)

a) Decrease basal insulin dose
b) Discontinue sulfonylurea
c) Discontinue all oral medications
d) Increase basal insulin dose
e) c) and d) only

Case Study: Hannah Three Months Later

- A_{1c}: 8.1%
- Fasting plasma glucose: 140 mg/dL
- Basal insulin titrated to 30 U/day
- She reports that afternoon hypoglycemia has subsided.
- Instruct her to titrate insulin dose upward to a target of 110 mg/dL as long as hypoglycemia is controlled.

Case Study: Hannah

6. After six months of insulin (titrated to 48 U/day), Hannah's fasting glucose has stabilized at 110 mg/dL. Her A_{1c} is 7.8%. You discuss with her the need to address her prandial blood sugar. Which of the following would be a suitable option at this point?

a) Continue current regimen with no changes
b) Restart sulfonylurea
c) Continue titrating basal insulin upward
d) Add mealtime insulin (basal-bolus) and discontinue DPP-4
e) b) and c) only

Case Study: Hannah Basal-Bolus Regimen

- Initiating basal-bolus regimen requires adjustment.
- Have Hannah monitor postprandial glucose for several days to determine which meal has greatest effect on blood glucose
- Recognize that basal may need to be reduced to accommodate bolus injection
- Give her options about scheduling injections
- Schedule follow-up in three months.

Case Study: Hannah

7. At her next visit, Hannah's A_{1c} is 6.9%, and her fasting glucose is 108 mg/dL. Her basal insulin dose is now 43 U/day. She reports several episodes of early-morning hypoglycemia. What is a possible option to provide additional flexibility while maintain the current level of efficacy?

a) Reduce basal insulin by 5 U/day
b) Consider a more concentrated basal insulin formulation (e.g., U-300 vs. U-100)
c) Discontinue bolus insulin
d) Consider adding a sulfonylurea
e) a) and c) only

Case Study: Hannah

Going forward, you should consider the following with Hannah:

- Arrange for her to receive counseling from a Certified Diabetes Educator and dietitian
- Schedule a follow-up visit in three months
- Advise her that continued self-monitoring of blood glucose is essential to maintain glycemic control.

Conclusions

- Type 2 diabetes is a progressive disorder that affects numerous organs and tissues.
- Achieving glycemic control is essential to manage diabetes and its complications.
- Management may require multiple antihyperglycemic agents with complementary mechanisms of action.
- Evidence-based guidelines recently issued by the ADA recommend basal insulin as an expedient means to achieve glycemic control.
- Basal insulins offer several advantages (e.g., extended duration of action, reduced peak effect).
- Next-generation basal insulins, including glargine U-300, provide the advantages associated with traditional basal insulin formulations but with reduced risk of hypoglycemia.

Questions

NJAFP
New Jersey Academy of Family Physicians