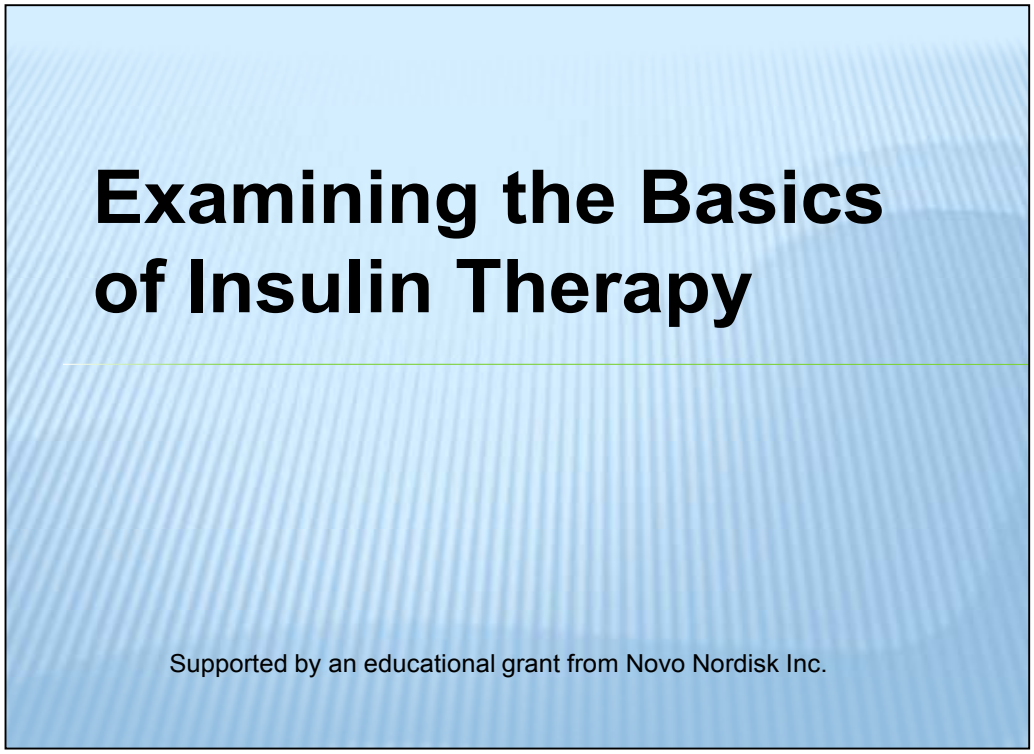
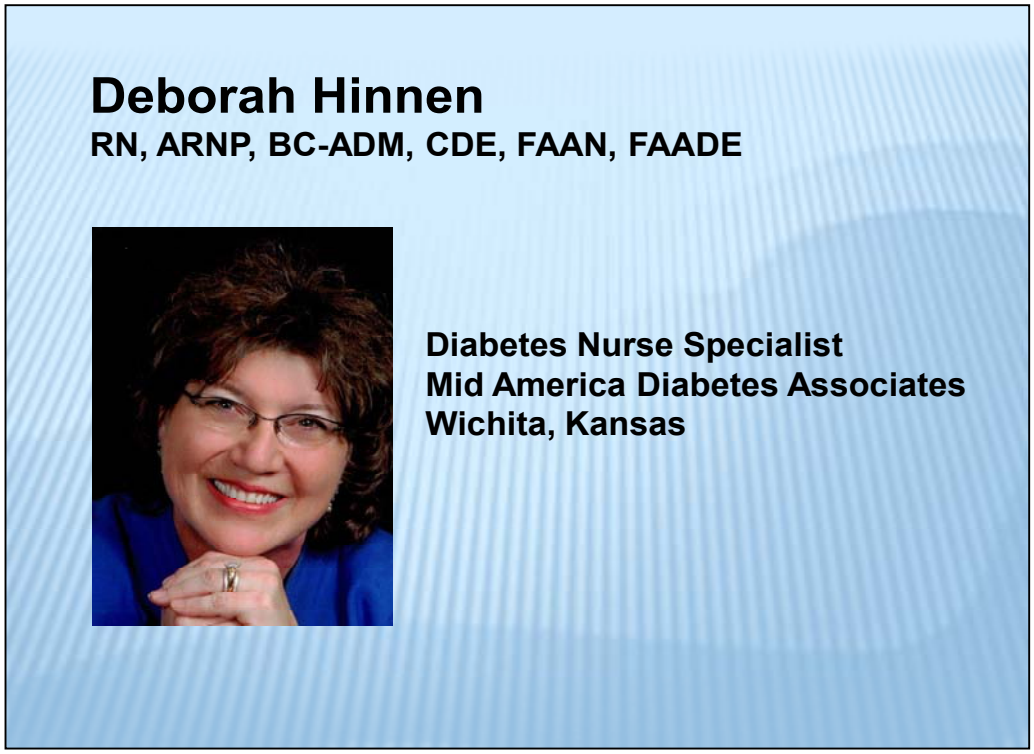


Examining the Basics of Insulin Therapy is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for nurses, pharmacists, and dietitians.



The following program is a recorded presentation by Deborah Hinnen.

Deborah Hinnen, RN, ARNP, BC-ADM, CDE, FAAN, FAADE has been a diabetes educator for over thirty years. As a clinical nurse specialist and education coordinator, she currently works at Mid America Diabetes Associates as coordinator of a multidisciplinary team. The centerpiece of their program is a three day comprehensive self-management course that serves nearly 1000 people with diabetes per year.

Ms. Hinnen is involved extensively with the American Association of Diabetes Educators (AADE), having served as their national President. She was awarded their prestigious Distinguished Service Award in the summer of 2001. She has also served on the national board of directors for the American Diabetes Association, and was an associate editor for *Diabetes Spectrum*. She continues to volunteer with many other organizations. Her faculty positions are with the Pharmacy Department at University of Kansas, Creighton and University of Nebraska and Graduate Nursing Department at Wichita State University and the Physicians Assistant Program at Wichita State. Ms. Hinnen was inducted as a Fellow into the American Academy of Nursing in 2003 and as a Fellow into the AADE in 2010.

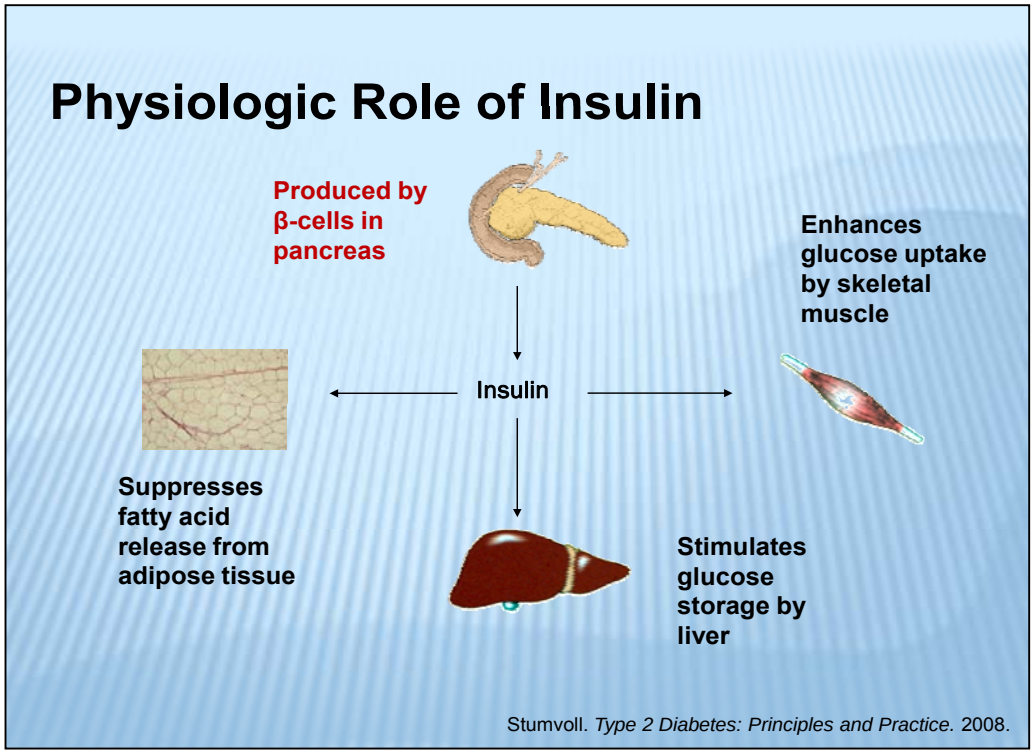
Her career has focused on diabetes patient and professional education with many publications in both areas. In addition to diabetes efforts, she served as a Trustee for Butler Community College, a college with seven sites and more than 14,000 students.

Objectives

- Describe the progressive physiologic changes that occur with type 2 diabetes, the benefits of maintaining target glycemic levels, and the role of insulin in these processes
- Discuss the various insulin products and insulin delivery devices currently available
- Explain the process of initiating and titrating insulin therapy in patients with type 2 diabetes

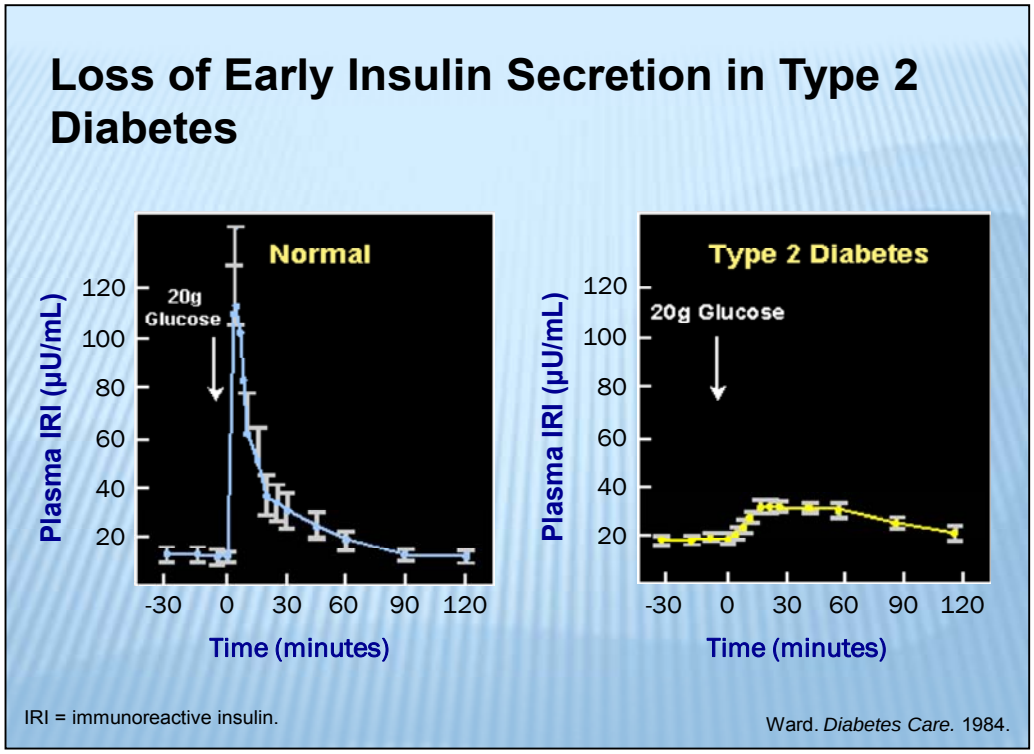
The objectives of this educational activity are to:

- Describe the progressive physiologic changes that occur with type 2 diabetes, the benefits of maintaining target glycemic levels, and the role of insulin in these processes
- Discuss the various insulin products and insulin delivery devices currently available
- Explain the process of initiating and titrating insulin therapy in patients with type 2 diabetes



Insulin, which is produced by β-cells in the pancreas, has a wide range of physiologic effects. It stimulates glucose storage by the liver, enhances glucose uptake by skeletal muscle, and suppresses fatty acid release from adipose tissue.

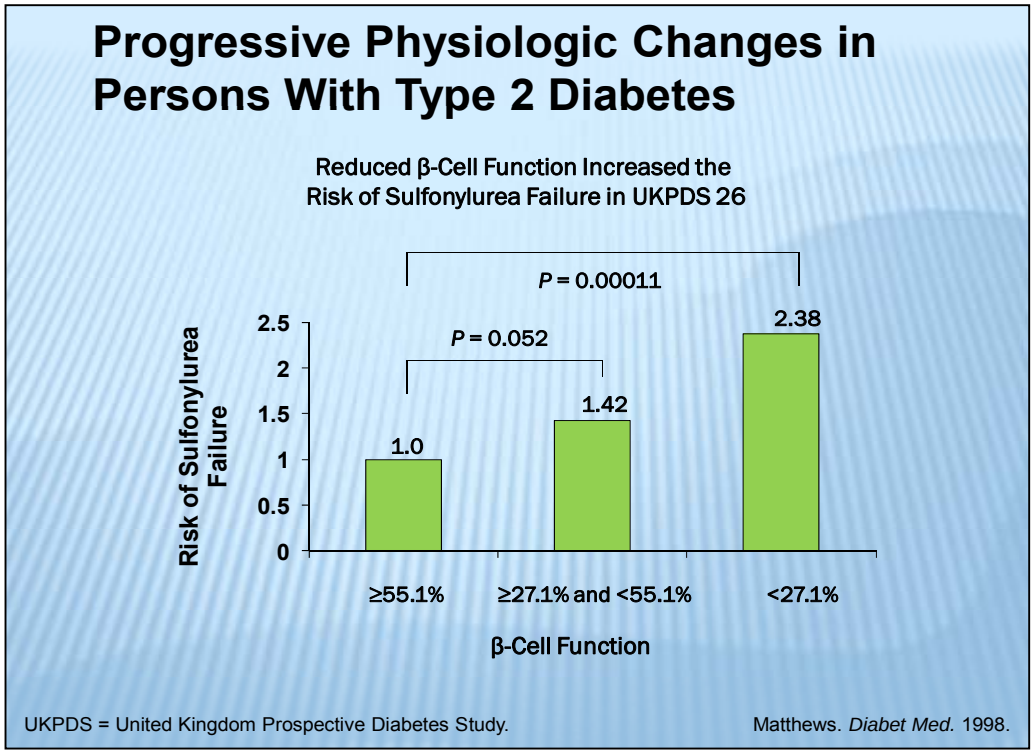
Insulin also stimulates the intracellular use of amino acids and inhibits the breakdown of glycogen, fat, and protein.



Laboratory studies have shown that physiologic responses to glucose administration are markedly different in persons without diabetes than in those with type 2 diabetes.

In people without diabetes, glucose-evoked insulin secretion is released from pancreatic β-cells in 2 phases. As illustrated by the graph on the left, individuals with normal β-cell function have an immediate, intense response to glucose administration that lasts for about 10 minutes. Following this first-phase response, they have a more moderate second-phase response that persists for 90 minutes to 2 hours after glucose administration.

People with type 2 diabetes experience a gradual deterioration of β-cell function that generally begins years before the development of diabetes symptoms and the diagnosis of diabetes. As shown by the graph on the right, this impairment of β-cell function often results in the loss of the first-phase response and the preservation of the second-phase response to glucose administration.



The major causes of type 2 diabetes are β-cell dysfunction, which causes impaired insulin secretion, and insulin resistance, which is manifested by increased glucose production by the liver and reduced peripheral glucose uptake. There is a reciprocal relationship between β-cell function and insulin sensitivity, since changes in one directly affect the other, although the relationship is not linear. Defects in insulin secretion appear before hyperglycemia develops, and these defects predict the progression from normal glucose tolerance to impaired glucose tolerance to diabetes. Longitudinal studies have shown that β-cell dysfunction rather than excessive body weight or insulin resistance predicts the progression to diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the progressive nature of reduced insulin secretion in newly diagnosed patients with type 2 diabetes. β-cell function, as measured by homeostasis model assessment (HOMA), showed a steady decline over time. This decline explains why most patients with type 2 diabetes eventually require insulin if they are to maintain or achieve their glycemic targets. Although patients in the UKPDS who were treated with sulfonylureas had an increase in β-cell function from 45% to 78% during the first year, their β-cell function later decreased along the same slope as that of the diet-treated group. Similarly, in the metformin group, β-cell function initially increased but declined from 66% to 38% by year 6. This slide shows the relationship between β-cell function and the ability of sulfonylurea therapy to maintain glycemic targets in the UKPDS population. Patients with the lowest level of β-cell function (<27.1%) had a risk of sulfonylurea failure that was 2.4 times that of patients with the highest level of function (≥55.1%).

Checkpoint 1

The correct statement is: _____.

a. insulin stimulates glucose release by the liver and suppresses fatty acid release from adipose tissue
b. patients with type 2 diabetes often retain the first-phase response to glucose administration
c. the major causes of type 2 diabetes are β-cell dysfunction and insulin resistance
d. in the UKPDS, β-cell function declined in patients with type 2 diabetes unless they received a sulfonylurea

The correct statement is: _____.

a. insulin stimulates glucose release by the liver and suppresses fatty acid release from adipose tissue
b. patients with type 2 diabetes often retain the first-phase response to glucose administration
c. the major causes of type 2 diabetes are β-cell dysfunction and insulin resistance
d. in the UKPDS, β-cell function declined in patients with type 2 diabetes unless they received a sulfonylurea

Answer to Checkpoint 1

The correct answer is **c**.

The major causes of type 2 diabetes are β-cell dysfunction and insulin resistance.

The correct answer is **c**.

The major causes of type 2 diabetes are β-cell dysfunction and insulin resistance.

Benefits of Maintaining A1C at Near-Physiologic Levels

Complication	Effect
Microvascular disease	Definitive evidence that lowering A1C to ≤7% reduces microvascular complications
Macrovascular disease	Inconsistent results in randomized controlled trials of intensive vs. standard glycemic control Follow-up of DCCT and UKPDS cohorts suggests that intensive treatment in years soon after diagnosis is associated with long-term reduction in macrovascular disease risk ("legacy effect")

DCCT = Diabetes Control and Complications Trial.

Skyler. *Diabetes Care.* 2009.

Randomized controlled trials have established that the risk of microvascular complications in patients with type 1 and type 2 diabetes can be reduced by intensive glycemic control (lowering the A1C to ≤7%). However, the potential for intensive glycemic control to reduce macrovascular (cardiovascular disease [CVD]) events has been less certain. The Action in Diabetes and Vascular Disease–Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT) showed no significant reduction in CVD outcomes with intensive glycemic control. One arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was stopped early when participants who received very intensive glycemic control (target A1C of <6%) experienced increased mortality.

In response to the results of ADVANCE, VADT, and ACCORD, the American Diabetes Association (ADA), American Heart Association, and American College of Cardiology published a joint statement about the relationship between intensive glycemic control and cardiovascular outcomes. The panel concluded that major trials of intensive versus standard glycemic control have not demonstrated significant CVD event reduction during their randomized phases. However, long-term follow-up of the Diabetes Control and Complications Trial (DCCT) and the UKPDS cohorts suggests that treatment to A1C targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in the risk for macrovascular disease. This long-term protective benefit of tight glycemic control soon after the diagnosis of diabetes is called the "legacy effect."

Current ADA and AACE Glycemic Goals

Parameter	ADA	AACE
A1C (%)	<7	≤6.5
Fasting/preprandial glucose (mg/dL)	70–130	<110
Postprandial glucose (mg/dL)	<180*	<140†

*Peak postprandial capillary plasma glucose. †2-h postprandial glucose.

- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals
- Goals should be individualized
- More or less stringent goals may be appropriate for individual patients

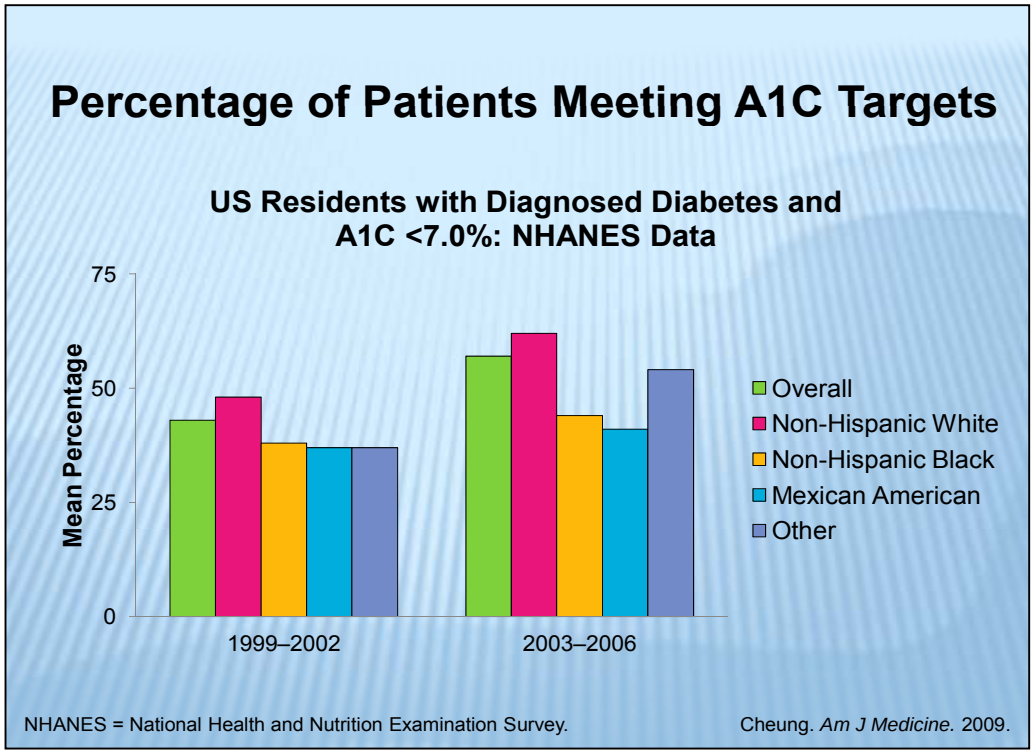
American Association of Clinical Endocrinologists. *Endocr Pract.* 2007.
American Diabetes Association. *Diabetes Care*. 2012.

This slide shows current evidence-based glycemic recommendations of the ADA and the American Association of Clinical Endocrinologists (AACE) for nonpregnant adults with diabetes. Some health care providers follow the ADA recommendations, while others prefer to use the AACE values.

The ADA has defined several key concepts for setting glycemic goals. A1C is the primary target for glycemic control. Postprandial glucose may be targeted if a patient does not meet A1C goals despite the attainment of preprandial glucose goals. Glycemic goals should be individualized based on the duration of diabetes, an individual's age and life expectancy, the presence or absence of comorbid conditions (especially cardiovascular disease and advanced microvascular complications), hypoglycemia unawareness, and individual patient preferences.

For selected individual patients, health care providers might reasonably suggest even lower A1C goals than the general goal of <7%, as long as this can be achieved without significant hypoglycemia or other adverse effects. Patients likely to benefit from more stringent goals are individuals with a short history of diabetes, long life expectancy, and no significant cardiovascular disease. In contrast, a less rigorous A1C goal might be appropriate for individuals with a long history of diabetes, a known history of severe hypoglycemia, severe atherosclerosis, and/or advanced age or frailty.

Although the glycemic goals recommended by the AACE differ somewhat from those recommended by the ADA, the principle of individualizing therapy based on patient characteristics also underlies the AACE guidelines.



Cheung and colleagues investigated whether glycemic control has improved in recent years among US adults with diagnosed diabetes. The investigators examined trends in A1C levels using National Health and Nutrition Examination Survey data for two periods, 1999 to 2002 and 2003 to 2006. As illustrated by the graph, the overall proportion of individuals attaining the ADA A1C target of <7% increased over time, from 43% to 57%.

This gradual improvement in mean A1C levels might have been caused by the adoption of more stringent A1C goals after publication of the results of the DCCT and the UKPDS, the availability of new drugs (eg, metformin, thiazolidinediones), improved patient education programs, and increased Medicare coverage for diabetes-related supplies.

A disturbing aspect of these findings is that, although average A1C levels are improving, many individuals still are not meeting optimal control targets, and A1C levels and rates of suboptimal control are especially high in some demographic groups. For example, about 56% of non-Hispanic blacks and 59% of Mexican Americans have A1C levels that exceed the ADA target.

Rationale for and Use of SMBG: ADA Recommendations

- Patients receiving multiple daily insulin injections or insulin pump therapy should perform SMBG ≥3 times daily
- May be useful guide to success of therapy for patients using less frequent insulin injections, noninsulin therapies, or MNT and physical activity alone
- May help patients to achieve postprandial glucose targets

MNT = medical nutrition therapy;
SMBG = self-monitoring of blood glucose.

American Diabetes Association. *Diabetes Care.* 2012.

According to the ADA, patients using multiple insulin injections or insulin pump therapy should perform self-monitoring of blood glucose (SMBG) 3 or more times per day. For patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy and physical activity alone, SMBG may be a useful guide to the success of therapy. Postprandial SMBG may help patients achieve their postprandial glucose targets.

When health care providers prescribe SMBG, they should ensure that patients receive initial instruction in monitoring techniques. Since the accuracy of SMBG is instrument and user dependent, it is important for health care providers to evaluate each patient's monitoring technique, not only initially, but also at regular intervals thereafter.

Because optimal use of SMBG requires proper data interpretation, patients should be taught how to use their blood glucose data to adjust food intake, exercise, or pharmacologic therapy to achieve their glycemic goals.

Benefits of Insulin Therapy for Patients With Type 2 Diabetes

- Insulin is most effective glucose-lowering agent
- Has many other beneficial effects
  - Improves pancreatic β-cell function
  - Increases hepatic and muscle insulin sensitivity
  - Lowers free fatty acids, reducing lipotoxicity
  - Increases HDL-C and decreases LDL-C
  - Reverses endothelial dysfunction
- Major adverse effects (hypoglycemia and weight gain) can often be minimized

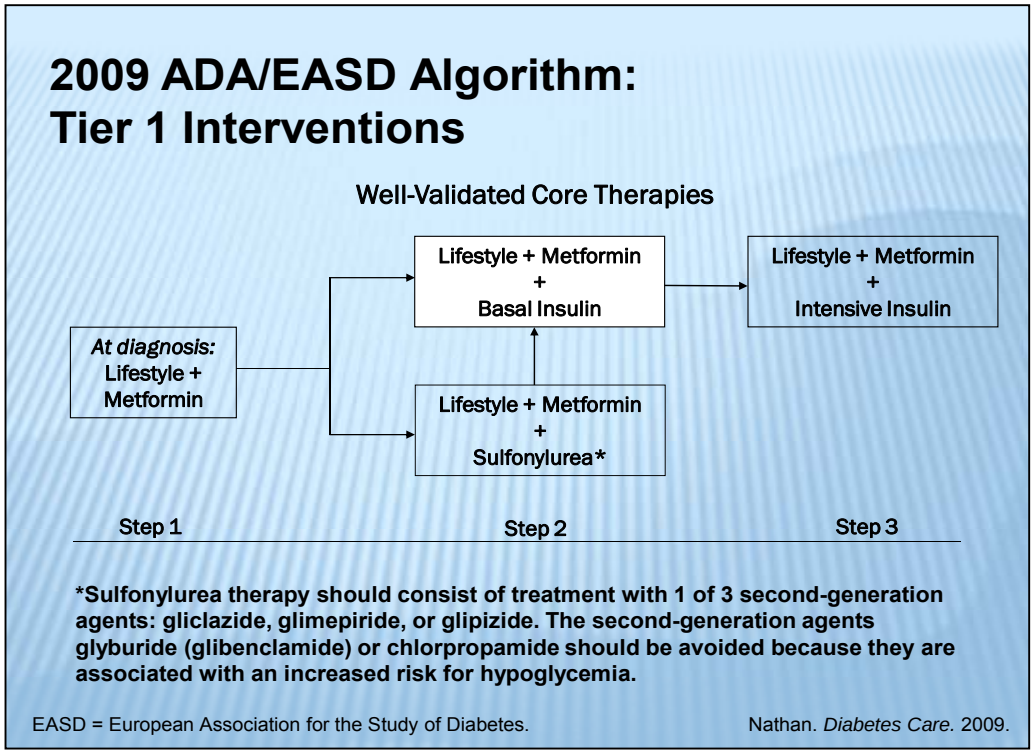
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Nathan. *Diabetes Care.* 2009. Bolli. *Diabetes Care.* 2011. Wyne. *Type 2 Diabetes: Principles and Practice.* 2008.

Among treatments for type 2 diabetes, insulin is the most effective at lowering glycemia. When used in sufficient doses, insulin can decrease any level of elevated A1C to, or close to, the therapeutic goal. Unlike other blood glucose-lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur.

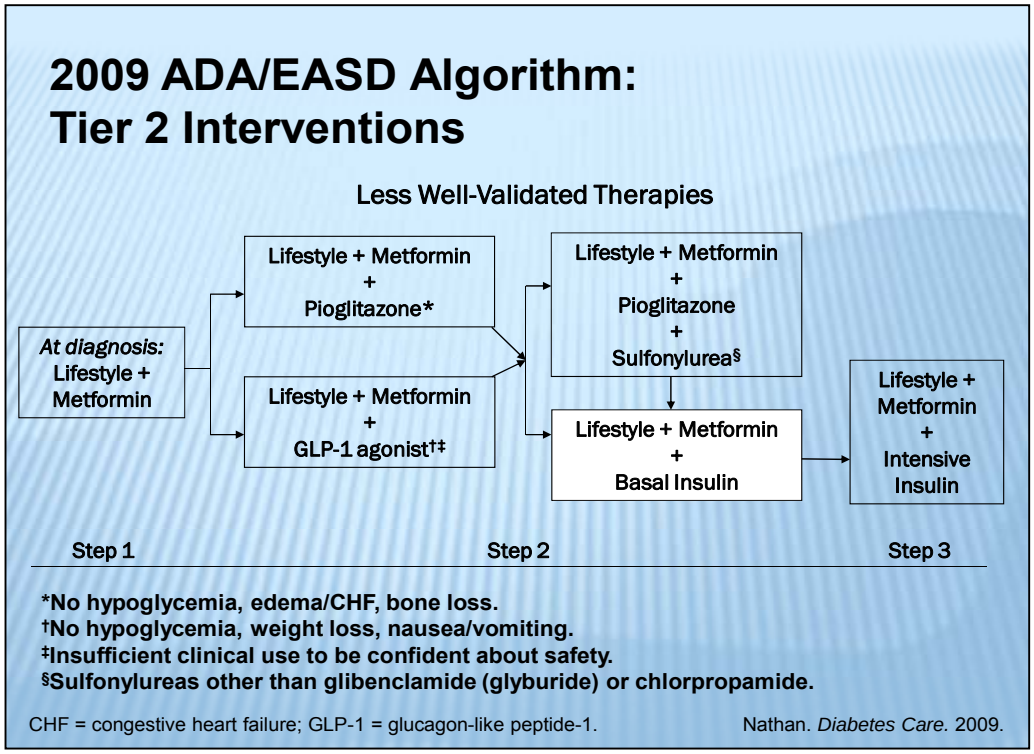
Insulin therapy also has many other beneficial effects. It addresses the two key deficits associated with type 2 diabetes by improving pancreatic β-cell function and increasing hepatic and muscle insulin sensitivity. It lowers free fatty acids levels, reducing lipotoxicity. Insulin also has beneficial effects on the cardiovascular system. It increases high-density lipoprotein cholesterol (HDL-C) levels and decreases low-density lipoprotein cholesterol (LDL-C) levels. It also reverses endothelial dysfunction.

The 2 major adverse effects of insulin therapy are hypoglycemia and weight gain. Patients can learn effective strategies for reducing the risk of developing hypoglycemia and for minimizing weight gain associated with the initiation or intensification of insulin therapy. These strategies will be discussed later in this activity.



"Medical Management of Hyperglycemia in Type 2 Diabetes" is a consensus algorithm for the initiation and adjustment of therapy that was developed by the ADA and the EASD and published in January 2009. A revised algorithm was published in the Spring of 2012. The algorithm has 2 tiers: the first includes well-validated core therapies and the second includes newer, less well-validated therapies. The basic principles underlying the algorithm are that health care providers should initiate metformin and reinforce lifestyle interventions at every visit and check A1C every 3 months until the A1C is <7% and then at least every 6 months. The interventions should be intensified if the A1C is ≥7%.

As shown in this slide, which depicts Tier 1 interventions, Step 1 consists of lifestyle modifications and metformin therapy at diagnosis. Insulin initiation at the time of diagnosis is recommended for individuals presenting with weight loss or other severe symptoms or signs of hyperglycemia. If Step 1 treatments do not achieve the patient's glycemic goals, another medication should be added within 2 to 3 months of the initiation of therapy or at any time when the target A1C level is not reached. At Step 2, basal insulin (a long-acting insulin analog or neutral protamine Hagedorn [NPH] insulin) should be added for a patient with an A1C level of >8.5% or with symptoms secondary to hyperglycemia. Other patients should receive a sulfonylurea (other than glyburide, which is associated with an elevated risk for hypoglycemia). Step 3 interventions consist of the initiation or the intensification of insulin therapy. Intensifying insulin therapy usually consists of additional injections, such as giving a rapid-acting insulin analog or a short-acting regular insulin before selected meals to reduce postprandial glucose excursions.

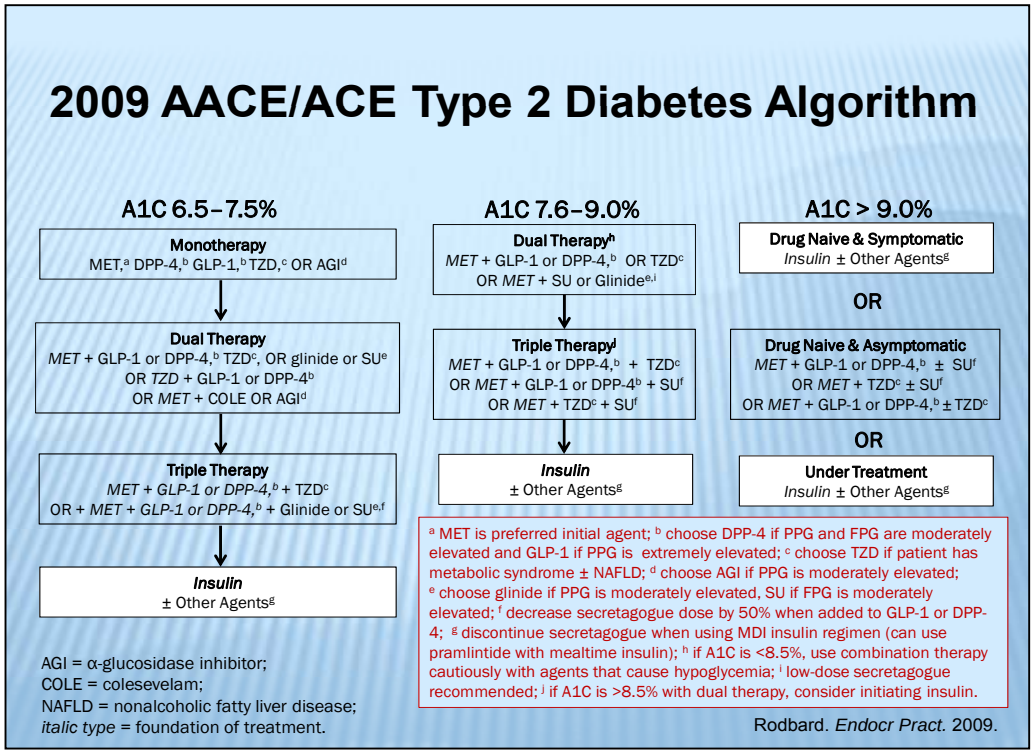


Tier 2 of the ADA/EASD algorithm presents less well-validated therapies that can be considered as Step 2 options in selected clinical settings. Specifically, when hypoglycemia is particularly undesirable (eg, in patients who have hazardous jobs), the addition of pioglitazone or a glucagon-like peptide (GLP-1) agonist may be considered.

An important advantage of pioglitazone is that it does not cause hypoglycemia. Peripheral edema is a frequent adverse effect, and pioglitazone-treated patients in clinical trials had a 2-fold increased risk for congestive heart failure. Patients who received pioglitazone for 5 years had a nonsignificantly higher risk of bladder cancer than those who had never received pioglitazone. Therefore, pioglitazone should not used in patients with active bladder cancer and should be used with caution in those with a prior history of bladder cancer. Bone loss may also occur. Although rosiglitazone, another thiazolidinedione, has also been approved for the treatment of type 2 diabetes, the consensus group unanimously advised against its use because of the possible increased risk for myocardial infarction. Currently, rosiglitazone is available in the US only through a limited-access program.

Like pioglitazone, the GLP-1 agonists (exenatide, liraglutide) do not cause hypoglycemia. They also cause moderate weight loss (eg, 2–3 kg over 6 months). Gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, occur commonly, especially at the start of treatment. Use of a GLP-1 agonist is preferable to treatment with pioglitazone when promotion of weight loss is a major consideration and the A1C level is close to target (<8.0%).

If these interventions are not effective in achieving the target A1C level or are not tolerated, the addition of a sulfonylurea other than glyburide could be considered. Alternatively, Tier 2 interventions could be stopped and basal insulin started.



This is the consensus algorithm for the treatment of type 2 diabetes developed by the AACE and American College of Endocrinology (ACE), published in September 2009. Underlying assumptions are that the target A1C is ≤6.5% and that the effectiveness of therapy should be evaluated every 2 to 3 months.

The algorithm stratifies patients into 3 groups according to their A1C at the time of presentation: 6.5% to 7.5%, 7.6% to 9.0%, or greater than 9.0%.

Insulin, given as monotherapy or in combination with additional glucose-lowering agents, is the initial treatment of choice for drug naive and symptomatic patients with an A1C greater than 9% and for patients whose A1C is greater than 9% despite ongoing therapy with other glucose-lowering agents.

Insulin with or without additional glucose-lowering agents is also recommended for patients who present with lower A1C values but do not reach the A1C target after receiving triple therapy with other agents.

Checkpoint 2

The correct statement is: _____.

a. according to the ADA/EASD algorithm, basal insulin therapy is a Tier 1, Step 2 intervention for type 2 diabetes

b. the ADA/EASD algorithm recommends a sulfonylurea for symptomatic patients with an A1C of >8.5% after initial metformin therapy

c. according to the AACE/ACE algorithm, all patients who present with an A1C of >9.0% should proceed to insulin therapy

d. the AACE/ACE algorithm recommends that all patients receive a trial of insulin monotherapy before other agents are added

The correct statement is: _____.

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b. the ADA/EASD algorithm recommends a sulfonylurea for symptomatic patients with an A1C of >8.5% after initial metformin therapy

c. according to the AACE/ACE algorithm, all patients who present with an A1C of >9.0% should proceed to insulin therapy

d. the AACE/ACE algorithm recommends that all patients receive a trial of insulin monotherapy before other agents are added

Answer to Checkpoint 2

The correct answer is **a**.

According to the ADA/EASD algorithm, basal insulin is a Tier 1, Step 2 intervention for patients with type 2 diabetes.

The correct answer is **a**.

According to the ADA/EASD algorithm, basal insulin is a Tier 1, Step 2 intervention for patients with type 2 diabetes.

Properties of Insulin

Insulin Type	Onset of Action	Peak	Duration of Action	Strength
Rapid-acting insulin analogs				
Insulin aspart	0–15 min	60–120 min	3–5 h	U-100
Insulin glulisine	0–15 min	60–120 min	3–4 h	U-100
Insulin lispro	0–15 min	30–90 min	3–6.5 h	U-100
Short-acting, regular, human	30–60 min	2–3 h	3–6 h	U-100
Intermediate-acting, NPH, human	1.5–4 h	4–12 h	12–18 h	U-100
Long-acting insulin analogs				
Insulin detemir	0.8–2 h	3.2–9.3 h*	≤24 h	U-100
Insulin glargine	1–2 h	flat	24 h	U-100
Regular, U-500, human	~30–60 min	~4–8 h	~24 h	U-500

NPH = neutral protamine Hagedorn.
*Dose dependent.

Sisson. *The Art and Science of Diabetes Self-Management Education Desk Reference.* 2011.
Humulin® R (regular U-500 [concentrated] insulin). Information for the physician. 2011.

Important properties of insulin products are their onset of action, peak, duration of action, and strength (concentration). These properties determine the individuals for whom the different preparations are prescribed and the situations in which they are used.

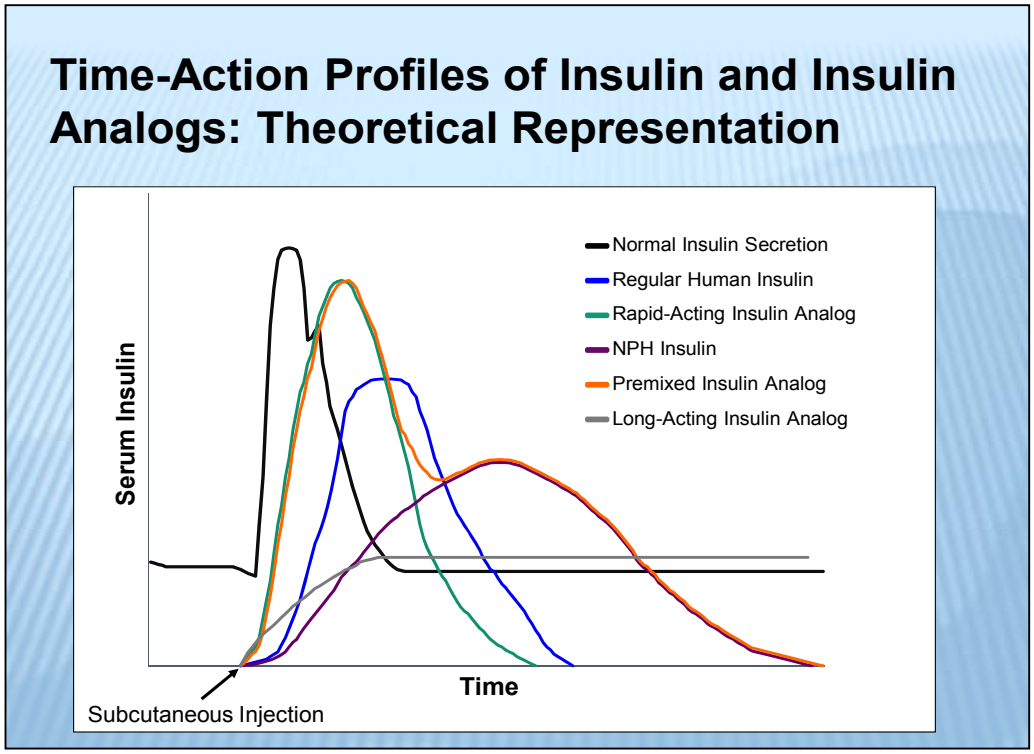
As shown on this slide, onset of action varies from 0 to 15 minutes for the rapid-acting insulin analogs to 1.5 to 4 hours for intermediate-acting (NPH) insulin.

Peak concentrations of the different preparations range from 1 to 2 hours for rapid-acting insulin analogs to 4 to 12 hours for NPH insulin. The long-acting insulin analogs are essentially peakless.

The duration of action of the various products ranges from 3 to 6.5 hours for the rapid-acting analogs to up to 24 hours for the long-acting analogs and U-500 insulin.

Except for U-500 insulin, all of the commercially available insulin preparations have a strength of U-100. U-100 insulins contain 100 units of insulin per milliliter of liquid, whereas U-500 insulin contains 500 units of insulin per milliliter of liquid.

The time course of action of any insulin may vary considerably among individuals or at different times within the same individual.



This theoretical representation compares the time courses of the various insulin preparations with the profile of normal (physiologic) insulin secretion. The profile of physiologic insulin secretion is plotted as the black line. The prandial component is represented by the peak, and the basal component is shown by the relatively flat line at either side of the peak. The dark blue line shows the time course of regular human insulin. As the graph shows, the pharmacokinetic profile of regular insulin does not reproduce the physiologic insulin profile. Compared with the prandial component of endogenous insulin, regular insulin is absorbed more slowly and declines to baseline more slowly. The green line shows the approximate time course of the rapid-acting insulin analogs. Compared with regular human insulin, the rapid-acting analogs more closely resemble prandial insulin secretion. Rapid-acting insulin analogs are absorbed and reach peak plasma levels, and also decline back to baseline, faster than regular human insulin. The purple line shows the time course of NPH insulin. Unlike the basal component of endogenous insulin, which has a flat action profile, NPH insulin peaks at 4 to 12 hours postinjection. The time course of NPH insulin is highly variable. The orange line shows the time course of the premixed insulin analogs. The rapid-acting component of the premixed insulin analogs closely reproduces the prandial component of physiologic insulin, but the long-acting component has a pronounced peak and therefore differs from the basal component of endogenous insulin. The gray line shows the approximate time course of the long-acting insulin analogs. Unlike NPH insulin and the long-acting component of the premixed insulin analogs, insulin glargine is nearly peakless, with a flat action profile. With insulin detemir, the peak effect is dose-dependent and reached between 3.2 and 9.3 hours post-administration. However, a constant level is found in the bloodstream during routine administration. This results in a plateau or basal effect that approaches 24 hours. Thus, both insulin glargine and insulin detemir more closely reproduce the basal component of physiologic insulin secretion when compared to NPH insulin and the long-acting component of the premixed insulin analogs.

Rapid-Acting Insulin Analogs and Short-Acting Insulin

- Rapid-acting insulin analogs
  - Insulin aspart (NovoLog®)
  - Insulin glulisine (Apidra®)
  - Insulin lispro (Humalog®)
- Short-acting insulin
  - Regular human insulin (Humulin® R, Novolin® R)
- According to the AACE/ACE algorithm, rapid-acting insulin analogs are preferable to short-acting insulins

Neithercott. *Diabetes Forecast*. 2012.
Rodbard. *Endocr Pract.* 2009.

Rapid-acting insulin analogs and short-acting insulin are used to manage the increases in blood glucose associated with meals. Therefore, they are used as components of multiple daily injection regimens, which mimic normal changes in insulin levels throughout the day.

Rapid-acting insulin analogs, which have an onset of action of 0 to 15 minutes, produce best results when injected 15 minutes before the start of a meal. Short-acting insulin, which has an onset of action of 30 to 60 minutes, is injected 30 to 45 minutes before a meal. According to the AACE/ACE consensus algorithm, rapid-acting insulin analogs are superior to short-acting insulin, providing a better, safer alternative for mealtime coverage.

The currently available rapid-acting insulin analogs are:

- Humalog® – insulin lispro injection, USP (rDNA origin)
- NovoLog® – insulin aspart (rDNA origin) injection
- Apidra® – insulin glulisine (rDNA origin) injection

The currently available short-acting insulins are:

- Humulin® R – regular insulin human injection, USP (rDNA origin)
- Novolin® R – regular human insulin injection (rDNA origin) USP

U-500 Insulin

- Highly concentrated insulin (500 units/mL vs 100 units/mL for other insulins)
- Intended for patients with marked insulin resistance (daily insulin requirement >200 units)
- Regular insulin, but often has time-action characteristics reflecting both prandial and basal activity
- Humulin® R (U-500) insulin is only commercially available formulation
- Never interchangeable with U-100 insulin
- Extreme caution must be used when drawing up dose

Cochran. *Diabetes Care.* 2005.
Humulin® R (regular U-500 [concentrated] insulin). Information for the physician. 2011.

Unlike other commercially available forms of insulin, which have an insulin concentration of 100 units/mL, U-500 insulin has a concentration of 500 units/mL. U-500 insulin is intended for the treatment of patients with marked insulin resistance (daily requirement >200 units), since a large dose may be administered subcutaneously in a reasonable volume. Persons most likely to benefit from U-500 insulin are individuals with genetic defects in insulin action, endocrinopathies, uncommon forms of immune-mediated diabetes, and other genetic syndromes associated with diabetes.

The one available U-500 insulin, Humulin® R (U-500) insulin, is unmodified by any agent that might prolong its action. Although U-500 insulin is available only as regular insulin, clinical experience has shown that it frequently has time-action characteristics reflecting both prandial and basal activity. It takes effect within 30 minutes, has a peak similar to that observed with U-100 regular human insulin, and has a relatively long duration of action (up to 24 hours) following single-dose administration because of the product's high concentration. However, as with other insulins, the time course of action of U-500 insulin may vary considerably among individuals or at different times within the same individual. In patients with insulin receptor abnormalities, the duration of U-500 insulin is even more prolonged due to an insulin degradation deficiency.

Injections of U-500 insulin are given at least twice daily, often before breakfast and dinner. Because U-500 insulin is highly concentrated, extreme caution must be observed when drawing up the dose. The manufacturer recommends that, when possible, U-500 insulin should be administered with a tuberculin syringe, which has volume rather than unit markings. Patients should be under constant medical supervision during treatment with U-500 insulin, and it is essential for them to understand that U-100 and U-500 insulin are never interchangeable. Although U-500 insulin costs more per milliliter than U-100 insulin or insulin analogs, the reduced volume of insulin administered translates into a reduced cost per unit of insulin compared with other insulin types. The only type of U-500 insulin currently available is Humulin® R (U-500) insulin.

Intermediate-Acting Insulin and Long-Acting Insulin Analogs

- Intermediate-acting insulin
  - NPH human insulin (Humulin® N, Novolin® N)
- Long-acting insulin analogs
  - Insulin detemir (Levemir®)
  - Insulin glargine (Lantus®)
- According to AACE/ACE treatment algorithm, long-acting insulin analogs are preferable to intermediate-acting insulins

Neithercott. *Diabetes Forecast*. 2012.
Rodbard. *Endocr Pract.* 2009.

Intermediate-acting (NPH) insulin and long-acting insulin analogs are used to mimic the action of endogenous basal insulin (that is, basal insulin produced by the body). NPH insulin and long-acting insulin analogs lower blood glucose between meals and overnight and are usually given once or twice daily. Since NPH insulin is a suspension, it requires extensive mixing to ensure consistent absorption.

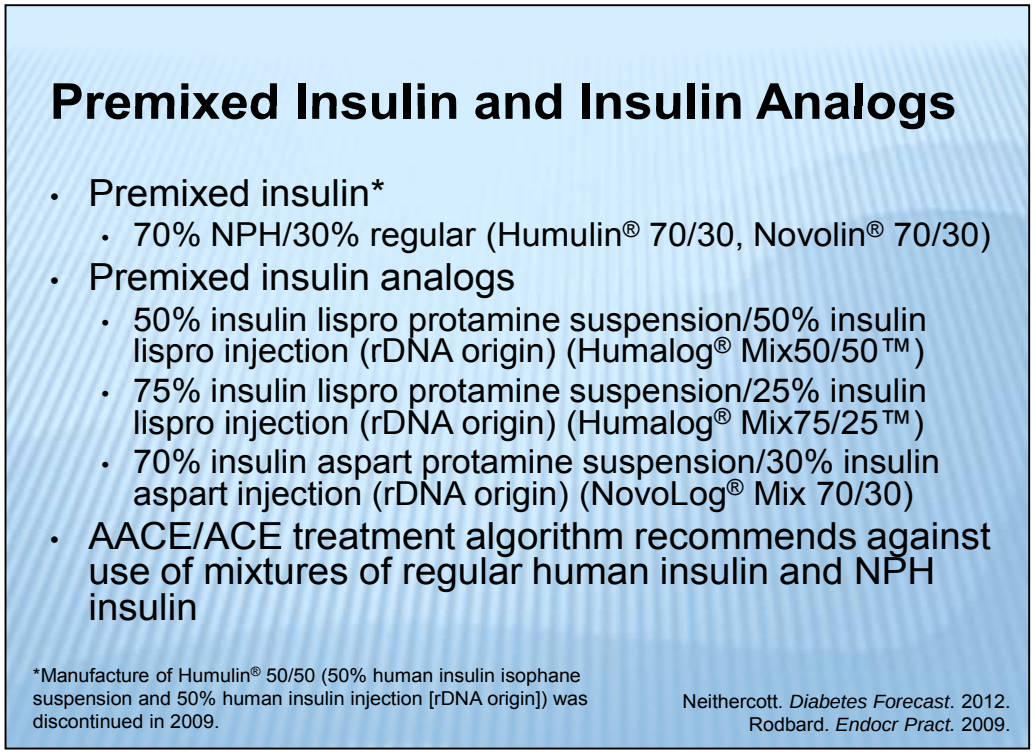
The currently available intermediate-acting insulins are:

- Humulin® N – NPH human insulin (rDNA origin) isophane suspension
- Novolin® N – NPH human insulin isophane suspension (rDNA origin)

The currently available long-acting insulin analogs are:

- Lantus® – insulin glargine (rDNA origin) injection
- Levemir® – insulin detemir (rDNA origin) injection

Insulin detemir and NPH insulin maybe used during pregnancy, whereas insulin glargine is a category C product. According to the AACE/ACE treatment algorithm, NPH insulin is not recommended, except during pregnancy. Use of NPH as a basal insulin has been superseded by insulin detemir and insulin glargine, which provide a relatively peakless profile for approximately 24 hours and yield better reproducibility and consistency, both between patients and within patients, and a corresponding reduction in the risk of hypoglycemia. Although the ACE/AACE treatment algorithm does not recommend NPH insulin, it is often prescribed for patients without prescription drug benefits, since it is less expensive than long-acting insulin analogs. NPH insulin is particularly inexpensive when purchased at a discount pharmacy.



Premixed insulin and insulin analogs were developed for patient convenience and are designed to approximate the profile of physiologic insulin. Premixed insulin formulations combine short-acting insulin with intermediate-acting insulin. Premixed insulin analog formulations combine a rapid-acting insulin analog with protamine, a small, arginine-rich nuclear protein that delays the onset and prolongs the duration of insulin action. Because all premixed formulations are suspensions, they require extensive mixing to ensure consistent absorption.

The currently available premixed insulin formulations are:

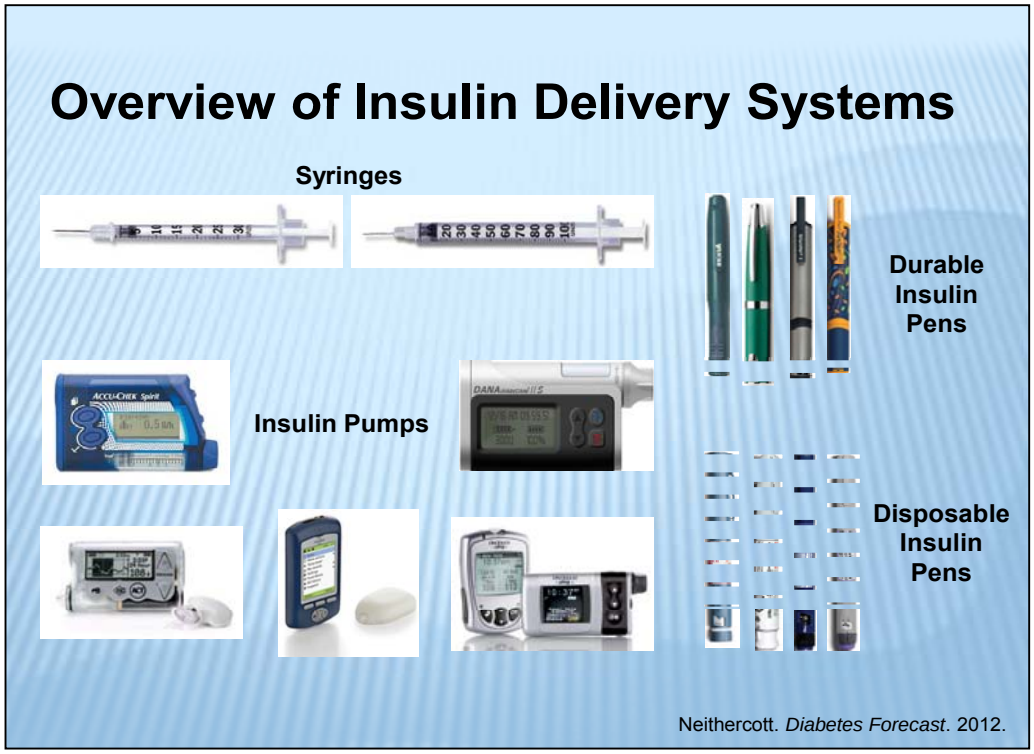
- Humulin® 70/30 – 70% human insulin isophane suspension and 30% regular, human insulin injection (rDNA origin)
- Novolin® 70/30 – 70% NPH, human insulin isophane suspension and 30% regular, human insulin injection (rDNA origin)

Manufacture of Humulin® 50/50 (50% human insulin isophane suspension and 50% human insulin injection [rDNA origin]) was discontinued in 2009.

The currently available premixed insulin analog formulations are:

- Humalog® Mix50/50™ – 50% insulin lispro protamine suspension and 50% insulin lispro injection (rDNA origin)
- Humalog® Mix75/25™ – 75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)
- NovoLog® Mix 70/30 – 70% insulin aspart protamine suspension and 30% insulin aspart injection (rDNA origin)

The AACE/ACE treatment algorithm recommends against using mixtures of regular human insulin and NPH insulin because maximal activity or regular does not occur until approximately 2 to 2.5 hours after injection. However, these products are often used for patients without prescription drug coverage because they are less expensive than premixed insulin analog formulations.



Major insulin delivery systems include syringes, durable and disposable insulin pens, and insulin pumps. For patients who use U-100 insulin, disposable insulin syringes with attached needles are available in 3/10 mL, 1/2 mL, and 1 mL syringe sizes and are chosen according to the insulin dose to be injected. Two needle lengths—12 mm (1/2 inch) and 8 mm (5/16 inch)—are also available. Traditionally, the 8 mm needle was recommended only for patients with a body mass index (BMI) less than 27 kg/m^2, but recent consensus guidelines recommend that all patients using a syringe use this needle to reduce the risk of injecting insulin into muscle. Standard syringe needles range from 28 gauge (G) to 31G. (Note that larger gauges signify finer needles, which generally cause less injection discomfort.) U-500 insulin should be administered with a tuberculin syringe because of the potential for error when dosing in units instead of milliliters.

Insulin pens are used by about 15% of US patients who treat their diabetes with insulin. The two basic types of insulin pens are durable (reusable) pens and disposable pens. Reusable pens deliver insulin via cartridges that are purchased separately, whereas disposable pens come with a non-removable cartridge. In addition to being portable, compact, and discreet, insulin pens may increase the accuracy of insulin dosing and increase adherence to the treatment regimen. Most patients who use an insulin pen can use extremely short, thin needles, typically reducing injection discomfort. Pen needles are available in 4 mm (32G), 5 mm (31G and 32G), 6 mm (31G), 8MM, and 12.5 mm sizes.

Today, less than 1% of patients with type 2 diabetes use an insulin pump (continuous subcutaneous insulin infusion [CSII]). An insulin pump is a one- or two-part device consisting of a reservoir filled with insulin, a small battery-operated pump, and a computer chip that allows the user to control insulin delivery. Some pump models infuse insulin through a length of tubing, while patch pumps deliver insulin through a cannula attached to the patch-type device.

Injecting Insulin With a Syringe

- Wash hands and cleanse injection site
- Examine insulin for clumping, roll vial if appropriate, and draw up dose
- Lightly grasp fold of skin (only if using ≥6 mm needle)
- Insert needle quickly at appropriate angle
- Push plunger in completely with slow, steady motion
- Dispose of syringe in accordance with local regulations

American Diabetes Association. *Diabetes Care.* 2004.
Frid. *Diabetes Metab.* 2010.

The preferred site for insulin injection is the abdomen (avoiding for a circle with a 2-inch radius around the navel). Insulin may also be injected into the subcutaneous tissue of the upper arm and the anterior and lateral aspects of the thigh, and the buttocks. Rotating the injection site is important for preventing lipohypertrophy or lipoatrophy. To reduce variability in insulin absorption from day to day, rotating within one area rather than rotating to a different area with each injection is recommended.

Before administering insulin, it should be checked for signs of damage (clumping, frosting, precipitation, or change in clarity or color). Rapid- and long-acting insulin analogs and short-acting insulin should be clear, whereas NPH insulin and premixed insulin should be uniformly cloudy. Detailed instructions on mixing insulin in preparation for injection are included in the ADA's 2004 guidelines on insulin administration. For all insulin preparations except rapid-acting insulin analogs, short-acting insulin, and insulin glargine, the vial or pen should be gently rolled in the palms of the hands to resuspend the insulin. An amount of air equal to the required dose of insulin should be drawn up and injected into the vial to avoid creating a vacuum. Next the insulin is drawn into the syringe, the fluid should be inspected for air bubbles, which can cause too small a dose to be given. One or two flicks of the forefinger against the upright syringe (needle pointing up) should allow the bubbles to move to the top of the syringe so that they can be expelled.

Injections should be made into the subcutaneous tissue. In most adults, a skinfold should be lifted only if a 6 mm or longer needle is being used. Generally, injections with 4- to 6-mm needles should be given at a 90-degree angle to the skin surface, whereas injections with a longer needle should be given at a 45-degree angle to avoid intramuscular injection, especially in the thigh area.

If an injection seems especially painful or if blood or clear fluid is seen after withdrawing the needle, the patient should apply pressure for 5 to 8 seconds without rubbing. Blood glucose monitoring should be done more frequently on a day when this occurs. Insulin syringes, needles, and lancets should be disposed of according to local regulations.

Injecting Insulin With a Pen

- Wash hands and cleanse injection site
- Attach new needle, roll cloudy insulin preparations
- Prime needle with 2 units of insulin, dial up dose
- Lightly grasp fold of skin (only if using ≥6 mm needle)
- Insert needle quickly at appropriate angle
- Firmly press injection button
- Keep needle in skin for 5–10 seconds
- Dispose of needle in accordance with local regulations

American Diabetes Association. *Diabetes Care.* 2004.
Frid. *Diabetes Metab.* 2010.

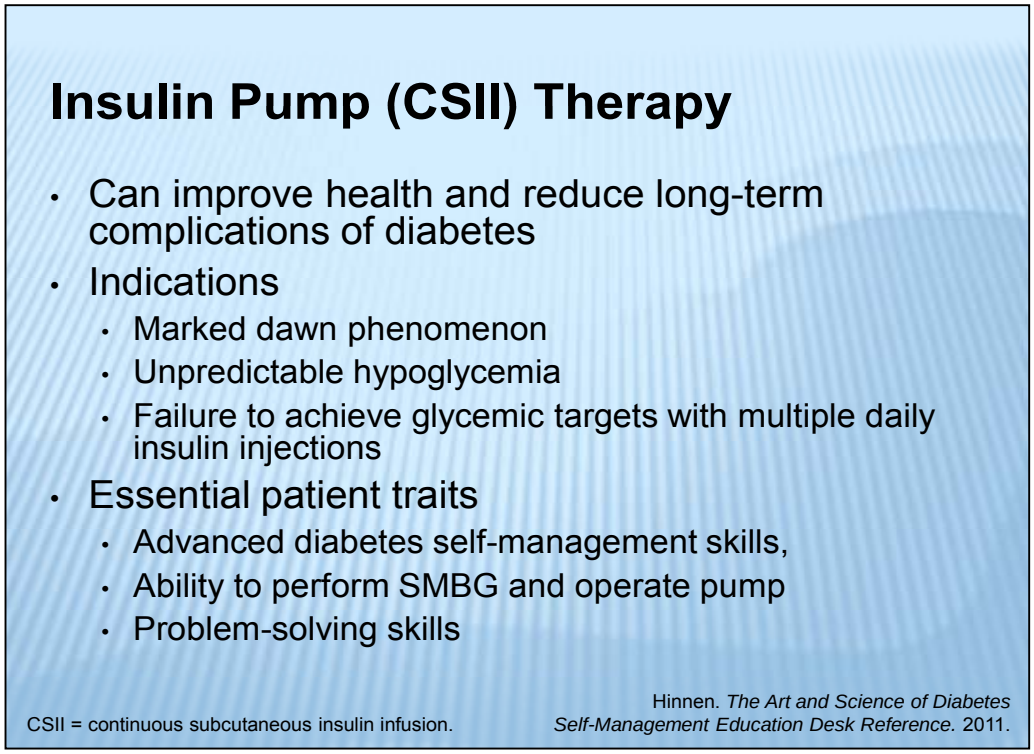
Before using their pen, patients should become familiar with the product information for the specific pen to be used. It is important to follow the manufacturer's instructions about needle attachment, dose selection and correction, and—for durable pens—cartridge insertion.

The process of administering insulin with a pen is generally similar to that of administering insulin with a syringe. If an NPH insulin or premixed insulin or insulin analog is being used, the insulin pen should be gently rolled in the palms of the hands to resuspend the insulin before injection.

Air bubbles are problematic because they can result in underdelivery of insulin. Air can enter the pen reservoir during manufacture or when the needle is left on the pen between injections. Therefore, patients should remove the pen needle and replace the pen cap as soon as they have finished an injection. They should also prime the needle with 2 units of insulin before each injection.

The main difference between administering insulin with a pen rather than with a syringe is what happens after the dose has been injected. After the patient presses the injection button of the pen, the needle should remain in the skin for 5 to 10 seconds to insure complete delivery of the dose. This brief delay in removing the needle is not necessary when using a syringe.

To prevent infections, insulin pen needles should not be reused and insulin pens should never be shared with another person.



The use of insulin pump (CSII) therapy to maintain normal or near-normal glycemia can improve patients' overall health and reduce the long-term complications of diabetes. Insulin pumps use rapid-acting insulin analogs or short-acting insulin. Insulin dosing is precisely delivered, to within one-hundredth of a unit.

One of the chief indications for pump therapy is marked dawn phenomenon. Dawn phenomenon consists of glucose elevation in the early morning hours before breakfast, which is caused primarily by overnight secretion of growth hormone and cortisol, along with increased insulin clearance. Other indications for pump therapy include a history of unpredictable hypoglycemia; failure to achieve glycemic targets with the use of 3 or 4 daily insulin injections; the desire for greater flexibility with regard to meal schedules, exercise, and travel; an unpredictable daily schedule; and pregnancy.

Essential traits of insulin pump users are the motivation to achieve and maintain glycemic targets; demonstration of advanced diabetes self-management skills; acceptance of day-to-day self-care responsibilities; realistic expectations about CSII therapy; the ability to practice SMBG and to use the insulin pump; demonstration of effective coping patterns and problem solving; and availability of support systems.

Contraindications to pump therapy are unrealistically high expectations about its benefits; severe depression or other serious behavioral disorders that might distract the individual from paying attention to details that are critical to successful pump therapy; and a history of inadequate self-care behaviors and health care practices.

Storing Insulin and Disposing of Sharps

- Storing insulin
  - Store all in-use insulin at room temperature (usually 59°F to 86°F)
  - Refrigerate all unopened vials, cartridges, and prefilled pens until use
  - Number of days that vial or pen can be used varies with insulin type and delivery system
- Disposing of sharps
  - Follow local regulations
  - Place used sharps in puncture-resistant container when community disposal programs are not available

American Diabetes Association. *Diabetes Care.* 2004.
Apidra® (insulin glulisine [rDNA origin] injection) solution for injection. Prescribing information. 2009.

All opened insulin should be stored at room temperature (usually 59°F to 86°F). However, insulin glulisine should not be stored above 77°F. In climates where room temperatures exceed the recommended ranges, opened vials can be stored in an insulated case or refrigerated and opened insulin pens should be stored in an insulated case, but not refrigerated. Unopened insulin vials, cartridges, and prefilled pens should be refrigerated until use. After first use, the number of days that a vial or pen can be used varies with the insulin type and delivery system. Therefore, it is important to check the package insert for each type of insulin used to determine this information. When taking the first dose of insulin from a new vial or pen that has been refrigerated, some individuals prefer to roll the syringe or pen in their hands to warm the insulin prior to administration.

Recapping, bending, or breaking a needle increases the risk of needle-stick injury and should be avoided. Insulin syringes and pens, needles, and lancets should be disposed of according to local regulations. Some areas may have special needle-disposal programs to prevent sharps from entering the main waste-disposal stream. When community disposal programs are not available, used sharps should be placed in a puncture-resistant container. Local trash authorities should be contacted for proper disposal of filled containers. In areas with recycling programs, placement of containers of used syringes, needles, and lancets with materials to be recycled is prohibited.

Checkpoint 3

The correct statement is: _____.

a. according to the AACE/ACE treatment algorithm, short-acting insulin and rapid-acting insulin analogs have similar benefits

b. of commercially available products, the long-acting insulin analogs have a time-action profile that most closely resembles that of endogenous insulin

c. vials and pens containing premixed human insulin should be rolled in the hands before use, but this is not necessary with premixed insulin analog products

d. to prevent lipoatrophy, the insulin pen needle should be removed from the skin as soon as the injection has been administered

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Answer to Checkpoint 3

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Basic Principles for Initiating Insulin Therapy

- The initial insulin regimen should be matched to the lifestyle, concerns, and capabilities of the individual patient
- The health care provider should be prepared to change regimens based on the patient's response and desires
- The patient is the key player in the diabetes care team and, if appropriate, should be trained and empowered to adjust medications to achieve glycemic goals and to prevent and treat hypoglycemia

Hirsch. *Clin Diabetes.* 2005.
Nathan. *Diabetes Care.* 2009.

When initiating insulin therapy, it is important to match the insulin regimen to the lifestyle, concerns, and capabilities of the individual patient. Although a basal-bolus regimen is the ideal treatment plan in terms of physiologic action and overall glycemic control, many patients are reluctant to start with so complex a regimen. Patients who are hesitant about undertaking basal-bolus management at the start of insulin therapy often make the transition to multiple daily injection regimens after gaining confidence in their ability to use insulin safely and effectively in less intensive regimens.

As a patient transitions to insulin therapy, the health care provider should be prepared to change regimens based on the patient's physiologic response to treatment and individual preferences.

The patient is the key player in the diabetes care team and, if appropriate, should be trained and empowered to adjust medications with the guidance of health care professionals to achieve glycemic goals and to prevent or treat hypoglycemia.

Strategies for Overcoming Psychological Resistance to Insulin

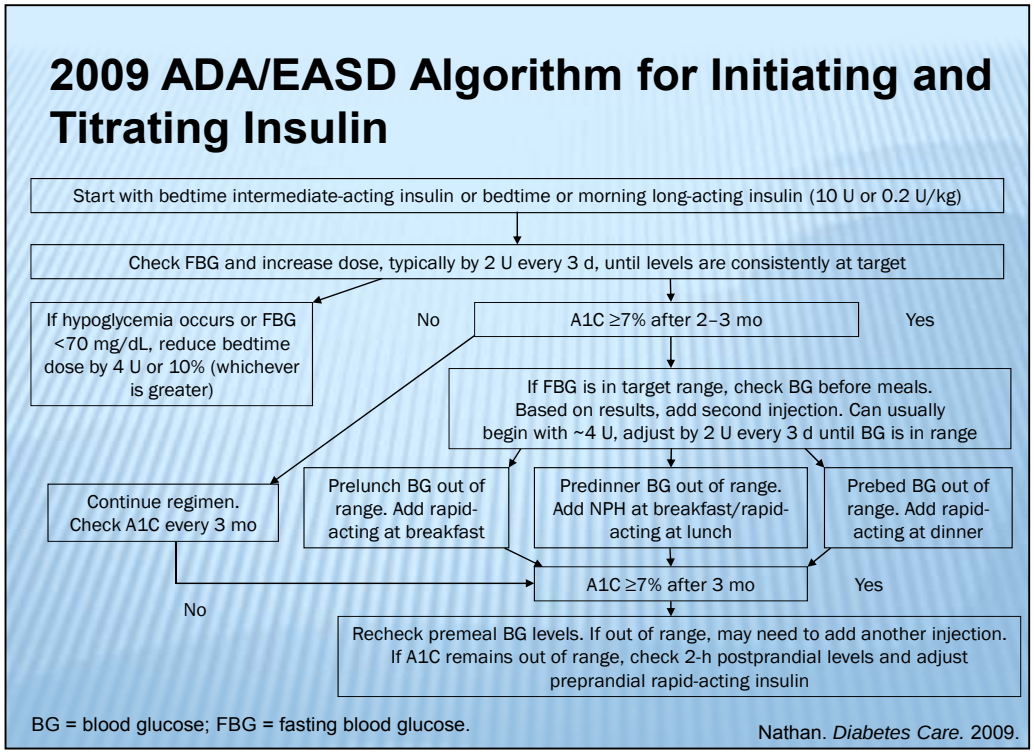
Concern	Response by Health Care Provider
Injection pain	Small, fine needles and other delivery systems reduce pain
Hypoglycemia	Effective strategies exist for preventing and promptly treating hypoglycemia
Weight gain	Changes in food intake, increased exercise, and continuing metformin therapy can minimize weight gain
Inconvenience	Newer tools and options permit patients to retain spontaneity and flexibility in their lives
Personal failure	Progressive β-cell dysfunction is a characteristic of type 2 diabetes

Peragallo-Dittko. *Diabetes Educ.* 2007.

"Psychological resistance to insulin" refers to the reluctance of patients and health care providers to initiate insulin therapy when it would be beneficial. The DAWN study, an international, cross-sectional survey that addressed barriers to diabetes management, showed that psychological resistance to insulin is common among patients and health care providers alike.

Peragallo-Dittko has described many strategies for reducing patients' psychological resistance to insulin. Informing patients about the small, fine needles and other delivery options that are currently available may lessen their fears about injection pain. Patients' concerns about hypoglycemia can be diminished by discussing strategies for reducing the risk for and the severity of hypoglycemia, such as practicing frequent blood glucose monitoring and recognizing and promptly treating hypoglycemic symptoms. In speaking with patients who are concerned about weight gain, health care providers can explain that changes in food intake and increased exercise can keep them from gaining weight. Continuing metformin therapy after insulin administration may also help to minimize weight gain. Patients concerned about the inconvenience of insulin therapy can be reassured that newer tools and options permit patients who use insulin to retain spontaneity and flexibility in their lives. In speaking with patients who equate beginning insulin therapy with personal failure, health care providers can explain that progressive β-cell dysfunction is a characteristic of type 2 diabetes.

By inviting patients to voice their concerns, engaging in active listening, and providing accurate information and emotional support, diabetes educators and other health care providers can facilitate the transition to insulin and contribute to a culture that encourages and supports the most effective diabetes management.



The 2009 ADA/EASD algorithm on the medical management of hyperglycemia in type 2 diabetes includes a separate algorithm for the initiation and adjustment of insulin regimens. It is based on recommendations in a 2005 publication by Hirsch and associates.

According to the ADA/EASD algorithm, insulin therapy can begin either with intermediate-acting insulin at bedtime or with a long-acting insulin analog at bedtime or in the morning. The suggested starting dose can be 10 units or 0.2 unit/kg. Based on the results of SMBG, the dosage can be increased every 3 days. Patients whose A1C is ≥7% after 2 to 3 months can add a second injection, depending on which of their values are out of range. Patients whose prelunch blood glucose is out of range can add a rapid-acting insulin analog at breakfast. Those whose predinner blood glucose is out of range can add NPH insulin at breakfast or a rapid-acting insulin analog at lunch. Those whose prebedtime blood glucose is out of range can add a rapid-acting insulin analog at dinner. For patients whose A1C remains ≥7% after 3 months and whose premeal blood glucose levels are out of range, it may be necessary to add a third injection. If the A1C still remains out of range, the health care provider should check 2-hour postprandial levels and adjust the dose of the patient's preprandial rapid-acting insulin analog.

Important messages of the ADA/EASD algorithm are that there are multiple ways to initiate insulin therapy and that meeting the patient's glycemic targets is likely to require considerable adjustment of the doses and types of insulin administered.

Commonly Used Insulin Regimens

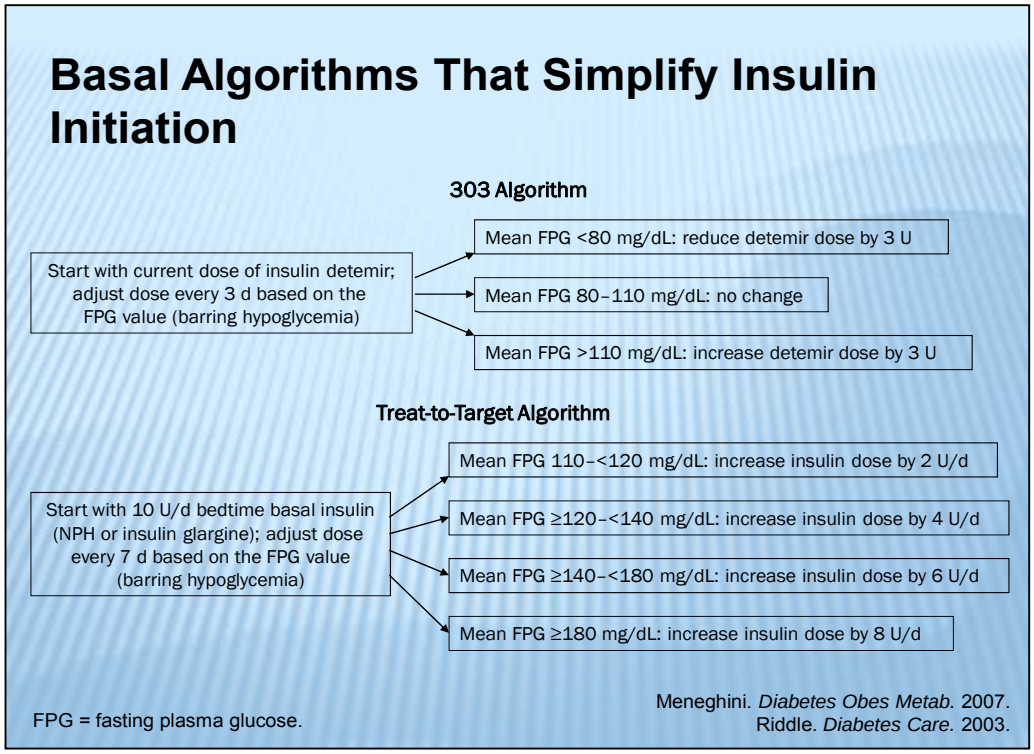
Regimen	Individual Most Likely to Benefit
Basal + oral agents	High FBG with minimal glucose rise during day
Premixed (biphasic) insulin	A1C >7% despite maximum-tolerated dosage of oral medications; glucose rises during day; patients requiring simpler regimen
Basal + bolus dose before most problematic meal	FBG in target range, but prelunch, predinner, or prebed BG out of range
Basal/bolus	FBG >250 mg/dL; any patient highly motivated to achieve tight glycemic control

Hirsch. *Clin Diabetes.* 2005.
Nathan. *Diabetes Care.* 2009.

This table shows the most commonly used insulin regimens. A regimen consisting of basal-only insulin plus oral agent(s) is appropriate for patients with high fasting blood glucose (FBG) with minimal glucose rise during the day. Because these patients eat small, regular meals, their postprandial glucose excursions are controlled adequately by oral medication.

When basal insulin plus oral medications do not keep postprandial glucose readings within target range (ADA less than 180, AACE less than 140), a twice-daily regimen using a premixed insulin preparation (prebreakfast, predinner) is an option. Premixed regimens are often chosen for patients who require a relatively simple insulin regimen. Health care providers can start patients on once-daily injections at the evening meal and add the second injection as needed. Premixed insulin consisting of a rapid-acting insulin analog and intermediate-acting insulin is an option if the patient eats small lunches or misses lunch regularly. A biphasic insulin preparation consisting of 70% NPH and 30% regular insulin would be appropriate for individuals eating large lunches, although patients following this regimen should eat lunch at about the same time each day to avoid hypoglycemia. In addition, they must wait 30 minutes after injecting insulin to eat their meal.

A “basal-plus” regimen, consisting of basal insulin with the addition of a bolus dose of rapid-acting insulin before the most problematic meal, is appropriate for patients whose FBG is at target but whose prelunch, predinner, or prebedtime BG is out of range. Basal/bolus therapy may be required for patients whose FBG exceeds 250 mg/dL. It is also appropriate for any patient who is highly motivated to achieve tight glycemic control.



Two basal algorithms that simplify the process of starting insulin are the 303 Algorithm and the Treat-to-Target Algorithm. The 303 Algorithm was used in the PREDICTIVE™ 303 Study. This 6-month study, which enrolled 5604 patients, evaluated the effectiveness of insulin detemir, using the patient self-adjusted dosing algorithm shown on this slide, compared with standard-of-care physician-driven adjustments. Insulin detemir was started once daily as add-on therapy to any other glucose-lowering regimens or as a replacement for prestudy basal insulin. At 26 weeks, the mean A1C decreased from 8.5% at baseline to 7.9% in the 303 Algorithm group and from 8.5% to 8.0% in the standard-of-care group. The between-group difference in A1C reduction was statistically significant. Mean fasting plasma glucose (FPG) values decreased from 175 mg/dL at baseline to 141 mg/dL for the 303 Algorithm group and decreased from 174 to 152 mg/dL for the standard-of-care group. Again, the between-group differences in FPG reduction were statistically significant.

The benefits of the Treat-to-Target Algorithm were shown in a 24-week clinical trial that enrolled 756 overweight patients who had an A1C of >7.5% during treatment with 1 or 2 oral agents. During the study, patients continued their oral agents and received bedtime insulin glargine or NPH insulin once daily, titrated using the algorithm shown on the slide. At end point, mean FPG was similar with glargine and NPH (117 vs. 120 mg/dL, respectively), and A1C levels were also similar (6.96% vs. 6.97%, respectively).

Regimens When Using Basal or Premixed Insulin

Most BG Levels (mg/dL) for Last 3–7 Days	Dosage Change (Units)
<80	–2
80–109	None
110–139	+2
140–179	+4
≥180	+6

- Adjust prebreakfast dose based on predinner/evening value.
- Adjust predinner (premixed)/bedtime (basal) dose based on prebreakfast/morning value.
- Do not increase dose if hypoglycemia (<70 mg/dL) or symptoms of hypoglycemia are present.

Hirsch. *Clin Diabetes.* 2005.

Timely dose titration is essential for successful insulin therapy. This slide shows a titration schedule developed by Hirsch and colleagues that can be used with once-daily and twice-daily regimens to make safe and timely insulin adjustments.

With this schedule, patients measure their blood glucose once or twice daily (prebreakfast, predinner), depending on their regimen. Based on data reported by the patient, the health care provider can make stepwise adjustments in response to average glucose values. Prebreakfast dose adjustments are based on predinner glucose results and predinner dose adjustments are based on prebreakfast glucose values. For example, if glucose is elevated predinner then the prebreakfast dose the next day should be increased.

During the dose-titration process, the patient should maintain weekly contact with the health care provider through visits or by communicating blood glucose monitoring data to the provider's office by telephone, fax, or e-mail. After reviewing the data, the health care provider can respond with instructions for dose adjustment.

If a patient is not at goal after 2 to 3 months of therapy or if recurrent hypoglycemia limits dose titration, the health care provider should consider changing the regimen.

Switching Regimens to Attain Glycemic Targets

Current Regimen	Switch to	Comments
Once-daily basal	Twice-daily premix	Give 50% of total daily dose prebreakfast* Give 50% of total daily dose predinner* Start 18–24 h after last basal dose
Once-daily premix	Twice-daily premix	Give 50% of total daily dose prebreakfast* Give 50% of total daily dose predinner*
Once-daily basal	Add rapid-acting insulin	Give 10% of total daily insulin dose as rapid-acting insulin (at largest meal) Reduce basal insulin dose by 10%
Twice-daily premix	Multiple daily injections	Divide total daily dose in half Initial basal dose = total daily dose/2 × 80% Initial prandial insulin dose = half of total daily dose × % of total estimated calories for each meal (eg, 35% of a 2000–calorie diet at lunch)

*Reduce total dose by 20% if patient experiences hypoglycemia.

Hirsch. *Clin Diabetes.* 2005.

This table presents suggestions developed by Hirsch and colleagues for switching from one insulin regimen to another.

For many patients, the transition to insulin therapy is smoothest when they begin with a single daily dose of insulin. As their confidence and experience increase, they are likely to accept a transition to twice-daily doses and eventually to a basal/bolus regimen.

Adding a rapid-acting insulin analog at the largest meal can serve as a bridge to basal/bolus therapy for a patient who is not attaining glycemic targets with once-daily basal insulin.

The next slide gives an example of a way in which these recommendations can be implemented.

Example of Switching Regimens to Attain Glycemic Targets

Baseline	GW's blood glucose levels values are above target during treatment with 60 units/day of premixed insulin analog, administered once daily
First adjustment	Administer 60 units of premixed insulin analog in 2 equal injections of 30 units, 1 before breakfast and 1 before dinner
Second adjustment	Switch to multiple daily injections using a long-acting and a rapid-acting insulin analog Initial basal insulin dose: 60 units/2 80% = 24 units Approximate daily calorie distribution: breakfast, 30%; lunch, 30%; dinner, 40% Initial rapid-acting insulin analog dose at breakfast and lunch: 30 units 30% = 9 units at each meal Initial rapid-acting insulin analog dose at dinner: 30 units 40% = 12 units

Hirsch. *Clin Diabetes.* 2005.

Here is an example of the process of switching regimens to attain glycemic targets following the recommendations of Hirsch and colleagues.

Greg Wright's blood glucose values are above target during treatment with 60 units per day of premixed insulin analog, administered once daily.

To achieve tighter control, Greg's health care provider recommended changing his insulin administration schedule from once daily to twice daily. With the new regimen, his 60 units of premixed insulin analogs were administered in two injections of 30 units, one given before breakfast and the other given before dinner.

After 2 months on this new regimen, Greg's blood glucose values were still not at target and he agreed to switch to a basal-bolus regimen using a long-acting insulin analog for basal coverage and a rapid-acting insulin analog for mealtime coverage.

Since Greg was receiving a total daily dose of 60 units of premixed insulin, his initial dose of long-acting insulin analog was calculated to be 60 units divided by 2, times 80%, or 24 units.

The approximate distribution of his daily calorie intake is 30% at breakfast, 30% at lunch, and 40% at dinner. Therefore, his initial dose of rapid-acting insulin analog would be 30 units times 30%, or 9 units at both breakfast and lunch. His initial dinnertime dose would be 30 units times 40%, or 12 units.

Based on the values recorded in his blood glucose log, Greg's basal-bolus regimen may need to be fine-tuned over the next several weeks.

Adjusting the Mealtime Insulin Dose

- Patients receiving multiple daily insulin injections can use advanced carbohydrate-counting skills to adjust their mealtime bolus dose
- The insulin-to-carbohydrate (ICR) ratio is used to match the dose of bolus insulin to carbohydrate consumption
- If the planned carbohydrate consumption is more (or less) than the amount typically consumed, the dose of prandial insulin is increased (or decreased) accordingly

Hinnen. *The Art and Science of Diabetes Self-Management Education Desk Reference.* 2011.

One technique that patients who receive multiple daily insulin injections can use to help keep their blood glucose levels at target is to adjust their mealtime bolus dose of rapid-acting insulin analog (or short-acting insulin) using advanced carbohydrate-counting skills.

A prerequisite to advanced carbohydrate counting is the determination of the individual's insulin-to-carbohydrate (ICR) ratio. The ICR is based on the principle that 1 unit of rapid- or short-acting insulin is needed to cover or match a specified amount of carbohydrate. The ratio is determined by calculating the individual's sensitivity to insulin. Whereas adults who are not overweight may have an ICR of 1:10 or 1:15, obese adults may have an ICR of 1:5.

The size of the mealtime bolus depends on the estimated number of grams of carbohydrate to be eaten at that meal. Training in advanced carbohydrate counting enables an individual to use the ICR to match the dose of insulin to planned carbohydrate intake. For example, Nancy Matthews, a patient with type 2 diabetes, has an ICR of 1:10 (1 unit of insulin to 10 grams of carbohydrate). Nancy usually consumes about 50 grams of carbohydrate at lunch, and therefore administers 5 units of her rapid-acting insulin analog before the meal.

Using the ICR: Example

- David Gonzalez, age 42 years
- Treats his type 2 diabetes with intensive insulin therapy
- ICR of 1:12
- With usual lunchtime carbohydrate consumption of 40 grams:

  40 g ÷ 12 = 3 units rapid-acting insulin analog
- If he planned to eat 50 grams of carbohydrate:

  50 g ÷ 12 = 4 units of rapid-acting insulin analog

Hinnen. *The Art and Science of Diabetes Self-Management Education Desk Reference.* 2011.

The case of David Gonzalez shows how an individual who has mastered the principles of advanced carbohydrate counting can use the ICR to match the dose of insulin to the planned carbohydrate intake.

David is a 42-year-old social worker. He was diagnosed with type 2 diabetes 6 years ago and has used intensive insulin therapy for the last year. His current ICR is 1:12 (1 unit of insulin to 12 grams of carbohydrate).

David usually consumes about 40 grams of carbohydrate at lunch, and, therefore administers 3 units of his rapid-acting insulin analog before the meal. (The calculation is 40 g divided by 12, which equals 3.3; this is rounded to 3 units.) However, if during his lunch at a pizzeria he planned to eat an additional 10 grams of carbohydrate, for a total of 50 grams, he would take 1 additional unit of insulin, for a total of 4 units. (The calculation is 50 g divided by 12, which equals 4.2; this is rounded to 4 units.)

Initiating Insulin Therapy in Patients With Special Needs

- Whenever possible, patient should self-administer insulin
- Many insulin delivery aids are available for people with visual impairments or limited manual dexterity
- Prefilled syringes are helpful for persons who depend on others to draw their insulin
- Insulin pens may improve accuracy of insulin administration for individuals with neurologic impairments

American Diabetes Association. *Diabetes Care.* 2004.

Whenever possible, insulin should be self-administered by the patient. Many insulin delivery aids, including nonvisual insulin measurement devices, syringe magnifiers, needle guides, and vial stabilizers, are available for people with visual impairments or limited manual dexterity. Information about these products is available in the ADA's annual Consumer Guide, which is published in the January issue of *Diabetes Forecast* magazine. Supplemental information is available online at forecast.diabetes.org.

Persons who depend on others to draw their insulin may benefit from prefilled syringes. Prefilled syringes are stable for up to 30 days when kept in a refrigerator. If possible, they should be stored with the needle pointing upward or lying flat, so that suspended insulin particles do not clog the needle. The prefilled syringe should be rolled between the hands before administration if the patient is receiving NPH or any other insulin combination. Neither insulin glargine nor insulin detemir should be mixed with any other insulin.

If the patient uses a mixture of insulins that is not commercially available as a premixed product, the insulins may be mixed by the caregiver. Syringes containing the mixed insulins can then be stored in the refrigerator. The health care provider should assess the effect of mixing insulins on glycemic control by reviewing a blood glucose log prepared by the patient or caregiver. When it is necessary to mix insulins, consistency of technique and careful SMBG are especially important.

Pen devices may improve the accuracy of insulin administration for individuals with neurological impairments, dexterity issues, and visual impairment.

Impact of Hypoglycemia

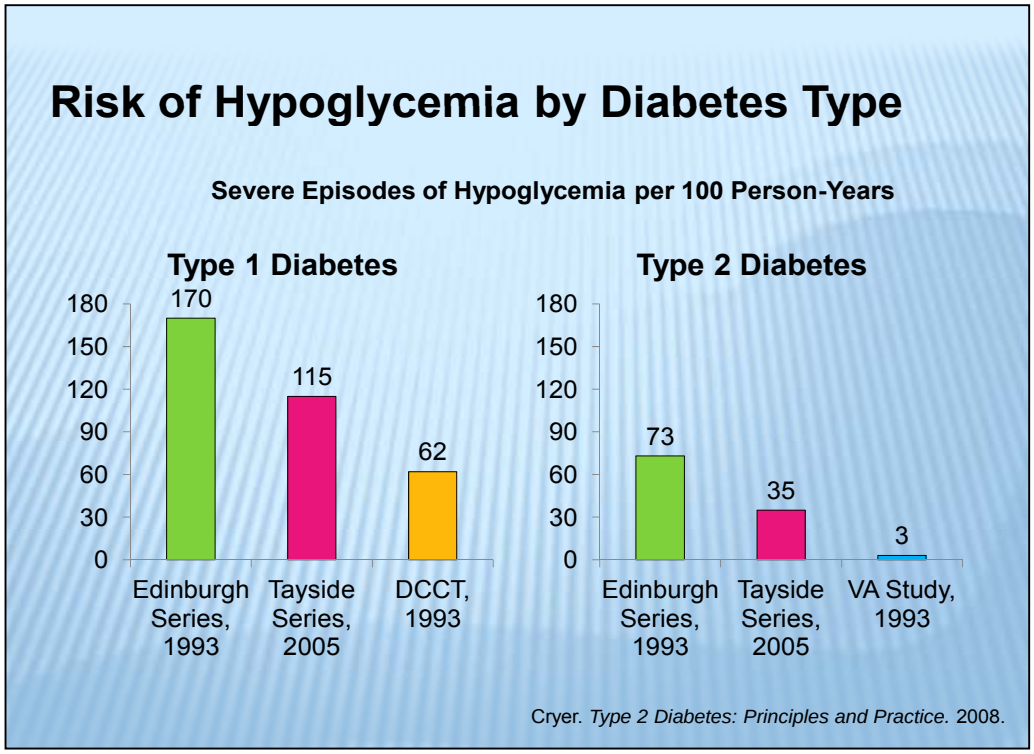
- Physical
  - Autonomic symptoms
  - Neuroglycopenic manifestations
  - Accidents
  - Acute cardiovascular events
- Psychological
  - Incapacitating fear and guilt about this fear
  - High levels of anxiety, low levels of happiness
- Social and occupational
  - Embarrassment
  - Social ostracism
  - Reduced workplace productivity

Cryer. *Type 2 Diabetes: Principles and Practice.* 2008.

As mentioned previously, concern about hypoglycemia is a major reason why many patients with type 2 diabetes are reluctant to transition to insulin therapy and many health care providers hesitate to prescribe it, even when it would improve the patient's glycemic control and overall health.

Hypoglycemia has negative physical, psychological, social, and occupational consequences. The physical morbidity of an episode of hypoglycemia includes unpleasant autonomic symptoms, such as sweating, hunger, palpitations, and anxiety. It may also include neuroglycopenic manifestations, such as cognitive impairment, behavioral changes, and, much less frequently, seizure, coma, and even death. While most patients experience complete neurologic recovery after an episode of hypoglycemia, prolonged, severe hypoglycemia can cause permanent neurologic damage. Hypoglycemia may result in falls and other accidents, including fatal traffic accidents.

Hypoglycemia can also result in psychological morbidity, including an incapacitating fear of experiencing hypoglycemia, guilt about this fear, high levels of anxiety, and low levels of happiness. Hypoglycemia can also lead to embarrassment, social ostracism, and reduced workplace productivity.



The graph on this slide shows rates of severe episodes of hypoglycemia, expressed in 100 person years, in representative populations of patients with type 1 and type 2 diabetes. As the graphs illustrate, the overall incidence of hypoglycemia is considerably lower in patients with type 2 diabetes than in those with type 1 diabetes. This occurs because patients with type 2 diabetes retain their defenses against falling blood glucose concentrations until late in the course of the disease.

Causes of hypoglycemia include: insulin or insulin secretagogue doses that are excessive or ill-timed; using the wrong type of insulin; decreased exogenous glucose delivery, such as after missed meals or snacks, or during an overnight fast; decreased endogenous glucose production, such as following alcohol ingestion; increased glucose utilization, such as during exercise; and decreased insulin clearance, such as in renal failure. Hypoglycemia may also be caused by increased insulin sensitivity due to treatment with an insulin sensitizer, exercise, weight loss, increased fitness, or tighter glycemic control.

Preventing Hypoglycemia During Insulin Therapy

- Reeducate patients about
  - Full spectrum of hypoglycemia symptoms
  - Factors contributing to hypoglycemia
- Increase SMBG frequency
- Address issue of hypoglycemia at every patient contact
- Investigate details of each hypoglycemic episode
- Prescribe long-acting insulin analog rather than NPH insulin and a rapid-acting insulin analog rather than short-acting insulin
- Initiate and titrate insulin with special care and consider modifying glycemic goals for high-risk patients
  - History of hypoglycemia or hypoglycemia unawareness
  - Multiple comorbidities
  - Advanced age, especially in patients with long history of diabetes

Cryer. *Type 2 Diabetes: Principles and Practice.* 2008.
Wolfsdorf JI. *Intensive Diabetes Management.* 2009.

Although the risk of hypoglycemia cannot be completely eliminated, it can be greatly reduced by taking several preventive measures.

At the time that insulin therapy is initiated or the regimen is changed, the health care provider should reeducate the patient about the full spectrum of hypoglycemia symptoms and factors associated with hypoglycemia.

The frequency of SMBG should be increased, based on the patient's regimen. In addition to regularly scheduled monitoring, the patient should be instructed to perform SMBG during and after a period of unaccustomed physical activity and before driving.

The health care provider should address the issue of hypoglycemia at every patient contact and thoroughly investigate the circumstances of each episode. Such an investigation will often suggest effective strategies for preventing future episodes.

Whenever possible, the health care provider should prescribe a long-acting insulin analog rather than NPH insulin and a rapid-acting insulin analog rather than short-acting insulin.

When treating a high-risk patient, the health care provider should initiate and titrate insulin with special care and consider adopting less stringent glycemic goals. Patients at particularly high risk for hypoglycemia include those with a history of severe hypoglycemia or hypoglycemia unawareness, those with multiple comorbidities, and elderly patients, especially if they have a long history of diabetes.

Weight Gain and Insulin Therapy

- Weight gain often accompanies insulin treatment
  - In 4-T Study, mean 3-year weight gain was 6.4 kg in prandial insulin group and 5.7 kg in premixed insulin twice-daily group
- Factors associated with weight gain
  - Failure to adjust for calories no longer lost via glycosuria
  - Consumption of extra calories to treat hypoglycemia
  - Repletion of body water and/or protein lost during periods of inadequate blood glucose control
  - Overeating due to ability to consume greater variety of foods without losing glycemic control

Holman. *N Engl J Med.* 2009;361:1736–1747.
Wolfsdorf JI. *Intensive Diabetes Management.* 2009.

Weight gain often accompanies insulin treatment. After 3 years of treatment in the 4-T Study, for example, the mean weight gain was 6.4 kg in patients who received prandial insulin therapy and 5.7 kg in those who received premixed insulin twice daily.

Several factors are associated with weight gain in insulin-treated individuals. Many patients who have an elevated A1C before starting insulin therapy are insulin depleted. Consequently, they do not metabolize food well and lose many calories through glycosuria, the excretion of glucose in the urine. After these patients begin treatment with insulin, an anabolic hormone, and become adequately insulinized, they metabolize nutrients more efficiently and glycosuria stops. However, these patients may not adjust their dietary intake for calories that had been formerly been lost via glycosuria.

After beginning insulin therapy, patients may also consume extra calories to treat episodes of hypoglycemia. Weight gain may result from repletion of body water and/or protein lost during a period of inadequate glucose control. Furthermore, patients who begin insulin therapy may overeat due to their ability to consume a greater variety of foods without losing glycemic control.

Preventing Weight Gain During Insulin Therapy

- Consider reducing caloric intake when initiating or intensifying insulin therapy
- Eliminate between-meal snacks
- Treat hypoglycemia with 15 grams of glucose (taken as glucose tablets or measured amount of carbohydrate)
- Initiate or increase physical activity
- Decrease insulin doses for activities that exceed daily routines, rather than snacking
- Teach flexibility in meal planning
- Continue taking metformin

Wolfsdorf JI. *Intensive Diabetes Management.* 2009.

There are many effective strategies for preventing weight gain in patients who are beginning or intensifying insulin therapy. Ideally, a weight-gain prevention plan should be developed jointly by the patient, the primary health care provider, and a registered dietitian, and should reflect the overall health and goals of the individual patient.

Because of the physiologic changes that accompany the initiation or intensification of insulin therapy, many patients need fewer calories than they previously did to maintain their weight or to lose weight safely. Detailed food and blood glucose logs kept by the patient are helpful in developing a new meal plan that meets all nutritional needs but contains fewer calories. Many patients who transition to basal-bolus insulin therapy benefit from consuming 250 to 500 calories less than they consumed previously.

For many patients, eliminating between-meal snacks is an effective way to reduce their caloric intake. The patient who consistently needs to eat snacks to avoid hypoglycemia may be using an excessive dose of basal insulin.

When hypoglycemia does occur, it should be treated with 15 grams of glucose (taken as glucose tablets or as a measured amount of carbohydrate). Treating hypoglycemia with foods that contain fat in addition to carbohydrate slows the correction of hypoglycemia and may result in excessive caloric intake.

If they have not already done so, patients should incorporate regular physical activity into their lifestyle. However, rather than eating more and therefore consuming additional calories when they exercise more than usual, patients should instead decrease their insulin dose. With practice and judicious use of SMBG, patients can become skilled at reducing their usual insulin dose to offset the effects of additional physical activity. Similarly, health care providers should teach flexibility in meal planning. Patients who use insulin should learn to reduce their food intake for convenience or weight control and to adjust their insulin doses accordingly. One of the benefits of metformin, which is often continued when patients transition to insulin therapy, is moderation of insulin-associated weight gain.

Checkpoint 4

The correct answer is: _____.

a. according to the ADA/EASD algorithm, 10 units of basal insulin is an appropriate initial dose for a patient who is starting insulin therapy

b. a patient with an ICR of 1:8 who will consume 40 g of carbohydrate at lunch should administer 8 units of rapid-acting insulin analog

c. insulins mixed by a patient or caregiver should be administered immediately and never stored for future use

d. after they transition to insulin therapy, patients may need to increase their calorie consumption modestly if they wish to maintain their weight

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Answer to Checkpoint 4

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Case Presentation: Introduction

- George Taylor, 57-year-old African American man
- Married, 2 children, 3 grandchildren
- Service manager at large car dealership
- Height, 70 inches; weight, 204 lbs (92.5 kg); BMI, 29.3 kg/m^2
- Inconsistent meal schedule and pattern
- Walks about 3 times per week for 30 minutes
- Lost 10 lbs over last 3 months

BMI = body mass index.

This case presentation illustrates the way that insulin therapy can be initiated and titrated in a patient with type 2 diabetes.

George Taylor presents for a visit to his primary health care provider. His last appointment was 3 months ago.

George is a 57-year-old African-American man. He is married and has 2 adult children and 3 grandchildren. He works as the service manager of a large car dealership in a suburb of a northeastern city. He is 70 inches tall, weighs 204 pounds, and has a BMI of 29.3 kg/m^2.

George says that he enjoys interacting with the customers at the dealership, but his work is often stressful and he has an unpredictable schedule. Depending on the volume of business, he eats lunch at any point between noon and 2 PM. He leaves work between 5:30 and 6:30, and sometimes does not sit down for dinner until 7:30.

Recently, he began walking with a neighbor for 30 minutes on Saturday and on 2 or 3 weeknights. He says that even these brief exercise sessions have made him feel more energetic and helped him to lose 10 pounds over the past 3 months. He reports that he has gradually learned to avoid the vending machine at work, with its high-fat, high-sodium snack foods.

Case Presentation: Clinical Summary

- Medical history
  - 6-Year history of type 2 diabetes
  - Hypertension
  - Dyslipidemia
- Medications
  - Metformin (1000 mg bid), glimepiride (4 mg/d), and sitagliptin (100 mg/d)
  - Lisinopril (20 mg/d)
  - Atorvastatin (20 mg/d)
  - Aspirin (81 mg/d)

George has a 6-year history of type 2 diabetes and also has hypertension and dyslipidemia. Otherwise, his health history is unremarkable.

Until recently, his glucose-lowering regimen consisted of metformin (1000 mg bid) and glimepiride (8 mg/day). Three months earlier, when his A1C was 8.4%, he also started taking sitagliptin (100 mg/day). At that point his glimepiride dose was reduced by 50%, to 4 mg/day.

George also takes lisinopril (20 mg/day), atorvastatin (20 mg/day), and aspirin (81 mg/day). He reports taking his medications consistently, and is not troubled by any side effects.

Case Presentation: Diabetes-Related History

- Laboratory values
  - A1C: current, 7.8%; 3 months ago, 8.4% (target: <7%)
  - Blood pressure: 124/76 mmHg (SBP target: <130 mmHg; DBP target: <80 mmHg)
  - LDL-C: 92 mg/dL (target: <100 mg/dL)
  - HDL-C: 43 mg/dL (target in men: >40 mg/dL)
  - Triglycerides: 138 mg/dL (target: <150 mg/dL)
  - GFR: 42 µg/mg (normal: <30 µg/mg)
- Diabetes-related issues
  - Sleep increasingly disrupted by need to urinate
  - Recent eye exam showed early signs of retinopathy

GFR = glomerular filtration rate.

American Diabetes Association. *Diabetes Care.* 2012.

Review of his laboratory values shows that George's current A1C is 7.8%, an improvement from 3 months earlier, when it was 8.4%. Clearly, his glucose control has improved with the switch from double to triple oral therapy, but his A1C is still above target.

With lisinopril 20 mg/day, his blood pressure is 124/76, and is thus in the target range. Similarly, with atorvastatin 20 mg/day, his plasma lipid values are at goal. Current levels are 92 mg/dL for LDL-C, 43 mg/dL for HDL-C, and 138 mg/dL for triglycerides.

His glomerular filtration rate is 42 µg/mg, indicating that George has renal insufficiency. In addition to this sign of early nephropathy, a recent eye examination showed signs of early retinopathy.

When the health care provider asks George about any diabetes-related problems, he replies that his sleep has been disrupted for the last several months by the need to urinate, sometimes 2 or 3 times per night.

Case Presentation: Initial Blood Glucose Log

Day	Before Bkfst	After Bkfst	Before Lunch	After Lunch	Before Dinner	After Dinner	Before Bed
Fri.	164	204	137	181	153	201	128
Sat.	172	199	131	185	166	197	135
Sun.	159	190	125	174	151	192	125

ADA glycemic recommendations: preprandial capillary plasma glucose, 70–130 mg/dL; peak postprandial capillary plasma glucose, <180 mg/dL.

American Diabetes Association. *Diabetes Care.* 2012.

In preparation for his appointment, George kept a detailed log of his blood glucose values for 3 days. Review of these values shows that George's fasting glucose levels consistently exceed the ADA's maximum preprandial value of 130 mg/dL. Likewise, his predinner levels are above the maximum preprandial value. All of his postbreakfast and postdinner levels exceed the ADA's maximum postprandial value of <180 mg/dL.

Several of his other BG levels also exceed the target range, and even the values that are within target are at the high end of the range.

Case Presentation: Insulin Initiation and Titration Following ADA/EASD Algorithm

- Treatment alternatives
  - Long-acting insulin analog at bedtime or in morning
  - Intermediate-acting insulin at bedtime
- Starting-dose alternatives
  - 10 units
  - 0.2 unit/kg 92.5 kg = 18.5 units
- Titration alternatives based on FBG level
  - Increase dose by 2 units every 3 days until levels are consistently in target range
  - Increase dose by 4 units every 3 days if FBG is >180 mg/dL
- George's glucose-lowering regimen
  - Long-acting insulin analog at bedtime, starting at 10 units, with 2-unit dosage increase every 3 days, to 50 units
  - Metformin 1000 mg bid
  - Glimepiride and sitagliptin discontinued

Nathan. *Diabetes Care.* 2009.

Despite improvement in his glycemic control over the past 3 months, George's health care provider recommends that he transition to insulin therapy at this point rather than attempting to bring his blood glucose values to goal with a different triple-therapy regimen. George, who is very concerned about his early signs of nephropathy and retinopathy, agrees that beginning insulin therapy is the best course of action for him.

Following the ADA/EASD insulin initiation algorithm, George's alternatives for beginning insulin are a long-acting insulin analog at bedtime or in the morning, or an intermediate-acting insulin at bedtime. George says he would rather take insulin in the evening instead of the morning, when he is often rushed to leave for work. The health care provider suggests that he use a long-acting insulin analog, since its time-action profile more closely resembles that of endogenous insulin and the risk of developing hypoglycemia is lower.

Based on the algorithm, starting-dose alternatives are 10 units per day or 0.2 unit per kilogram. Since George weighs 204 pounds (92.5 kg), his starting dose according to the unit-per-kilogram method would be 18.5 units. The health care provider instead chooses a starting dose of 10 units for George. According to the algorithm, titration alternatives are increasing the dose by 2 units every 3 days until levels are consistently within the target range, or increasing the dose by 4 units every 3 days if the FBG level is >180 mg/dL. Since George's FBG levels range from 159 to 172 mg/dL, increasing the dose by 2 units is the appropriate choice.

Thus, George's initial insulin regimen is a long-acting insulin analog at bedtime, starting at a dose of 10 units, with a 2-unit increase every 3 days. His dosage is eventually titrated to 50 units.

The health care provider cautions George that he should reduce his bedtime dose of long-acting insulin analog by 4 units or 10% (whichever is greater) if he experiences an episode of hypoglycemia or an FBG level of <70 mg/dL. George will continue to take metformin 1000 mg twice daily, but will discontinue taking glimepiride and sitagliptin. To ensure that the titration process goes smoothly, he will return to the health care provider's office once a week for the next several weeks.

Case Presentation: Blood Glucose Log After 3 Months

Day	Before Bkfst	After Bkfst	Before Lunch	After Lunch	Before Dinner	After Dinner	Before Bed
Fri.	108	144	121	188	148	192	117
Sat.	113	155	126	192	146	197	122
Sun.	117	150	122	185	146	199	120

American Diabetes Association glycemic recommendations: preprandial capillary plasma glucose, 70–130 mg/dL; peak postprandial capillary plasma glucose, <180 mg/dL.

American Diabetes Association. *Diabetes Care.* 2012.

After 3 months, George has made additional progress toward improving his overall health and reaching his glycemic goals. He has continued to avoid unhealthy food choices and has lost 8 more pounds. His BMI has decreased to 28.1 kg/m^2. He and his neighbor now walk for 30 minutes five days a week.

His current A1C is 7.4%, a reduction from 7.8% three months earlier and from 8.4% six months earlier.

George reports that the process of adjusting to insulin therapy was easier than he expected. He is especially pleased that he has continued to lose weight while taking insulin, has more energy, and is making fewer trips to the bathroom in the middle of the night. He has not experienced any symptoms of hypoglycemia and has not had any SMBG readings near or below 70 mg/dL.

Review of George's blood glucose log at the 3-month follow-up confirms that he has made considerable progress toward reaching his glycemic goals. His fasting glucose levels are at target, ranging from 108 to 117 mg/dL. His postbreakfast, prelunch, and bedtime values are also within range. However, his postlunch values are modestly elevated and his pre- and postdinner values are more substantially elevated.

The results of George's most recent A1C test and his blood glucose data show that his treatment regimen requires further adjustment.

Case Presentation: Treatment Alternatives at 3 Months (1)

- Switch from once-daily basal insulin to twice-daily premixed insulin
  - Divide total daily dose (50 units) in half
  - Give prebreakfast and predinner premixed insulin (25 units before each meal)
  - Titrate to goal, with a larger proportion at the largest meal (dinner)
  - Continue taking metformin (1000 mg bid)

Hirsch. *Clin Diabetes.* 2005.

One treatment alternative for George, which has been described by Hirsch and colleagues, is to switch from once-daily basal insulin to twice-daily premixed insulin.

To make this transition, George's total current daily dose of long-acting insulin analog (50 units) would be divided in half. George would begin by taking 25 units of premixed insulin before breakfast and 25 units before dinner. From this baseline, he would titrate to goal, eventually taking a larger proportion of premixed insulin at dinner, his largest meal.

George would continue taking metformin at a dose of 1000 mg bid.

Case Presentation: Treatment Alternatives at 3 Months (2)

- Add rapid-acting insulin analog at largest meal (dinner)
  - Give 10% of total daily dose (50 0.10 = 5 units) as rapid-acting insulin analog at dinner
  - Reduce 9 PM long-acting insulin analog dose by 10% (50 0.10 = 5 units; 50 – 5 = 45 units)
  - Continue taking metformin (1000 mg bid)
  - Adjust predinner dose of rapid-acting insulin analog as needed (after further education)

Hirsch. *Clin Diabetes.* 2005.

A second treatment alternative for George, which has also been described by Hirsch et al, is to add a rapid-acting insulin analog at his largest meal (dinner). Following this regimen, George would give 10% of his total daily insulin dose (5 units) as a rapid-acting insulin analog at dinner. He would reduce his 9 PM long-acting insulin analog dose by 10%, to 45 units. He would continue taking metformin 1000 mg bid. He would also begin an educational program to learn advanced carbohydrate-counting skills. With these skills, he would be able to modify his predinner dose of rapid-acting insulin analog to match the carbohydrate content of his meals.

When asked for an opinion about the better alternative for him, George's health care provider recommends adding a bolus dose of rapid-acting insulin analog at dinner. Since the β-cell destruction that characterizes type 2 diabetes is progressive and since George is relatively young and healthy, it is likely that he will eventually need to adopt a multiple daily injection (MDI) regimen to keep his glycemic values at goal. A "basal-plus" regimen is a good way to transition from a basal-only regimen to an MDI regimen.

George agrees that switching to a basal-plus regimen and pursuing advanced diabetes self-management education would be in his best long-term interest.

Case Presentation: Blood Glucose Log After 6 Months ("Basal-Plus" Regimen)

Day	Before Bkfst	After Bkfst	Before Lunch	After Lunch	Before Dinner	After Dinner	Before Bed
Fri.	96	133	108	143	111	133	82
Sat.	93	129	117	152	115	127	102
Sun.	95	128	111	141	108	131	76

American Diabetes Association glycemic recommendations: preprandial capillary plasma glucose, 70–130 mg/dL; peak postprandial capillary plasma glucose, <180 mg/dL.

American Diabetes Association. *Diabetes Care.* 2012.

Three months after switching to a basal-plus regimen, at his 6-month follow-up visit, George reports several accomplishments. He has lost 5 more pounds and, at 191 pounds, has a BMI of 27.4 kg/m^2. He says that he is continuing to feel more energetic. In addition to walking with his neighbor, he has joined a local gym and now walks or works out for 45 minutes five times per week. George has nearly finished his advanced diabetes self-management classes and demonstrates proficiency in carbohydrate counting and adjusting his dose of rapid-acting insulin analog based on his ICR (1:8) and the carbohydrate content of his evening meal.

Review of George's blood glucose log confirms that he has made excellent progress toward achieving his glycemic goals and that all of his blood glucose levels are now within the target range. However, 2 bedtime readings (76 and 82 mg/dL) are approaching the hypoglycemic range.

When asked about these low readings, George reports that he had exercised at the gym on both evenings. He says that although he felt unusually tired when he went to bed, he had attributed his fatigue to his vigorous workouts. The health care provider supports George's commitment to his exercise program and suggests that he take less insulin at dinner when he plans to go to the gym after dinner. He might consider changing his ICR from 1:8 to 1:12 on his gym nights. Changing the ratio and taking less insulin is preferable to his other option, a bedtime snack. By changing the ratio, he does not need to consume unnecessary calories to keep his BG in the normal range. Thus he reduces the risk of gaining weight with his more intensive insulin regimen.

Summary

- Type 2 diabetes is characterized by progressive β-cell dysfunction and insulin resistance
- Maintaining the A1C at near-physiologic levels reduces microvascular complications of diabetes and may also reduce the long-term risk of macrovascular complications
- Insulin is the most effective glucose-lowering agent and has many other beneficial effects
- Many different insulin products and delivery systems are available to meet the specific needs of individual patients
- A number of algorithms have been developed to facilitate the initiation and titration of insulin therapy
- Effective strategies for minimizing the risks of hypoglycemia and weight gain in insulin-treated patients are available

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