Comparing Normal Insulin Physiology and Insulin Dysfunction in Diabetes Mellitus: Constructing Optimal Insulin-Based Regimens

Jointly provided by

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TARGET AUDIENCE
This activity is intended for endocrinologists/diabetologists and other healthcare professionals who manage diabetes mellitus.

PURPOSE
The overall goal of this activity is to provide learners with a thorough understanding of insulin physiology and its dysfunction seen in diabetes mellitus (DM), an overview on current and emerging insulin therapies, and best practices on constructing insulin-based treatment regimens to improve outcomes for patients with DM.

ACTIVITY OVERVIEW
The Centers for Disease Control and Prevention estimates that 9.3% of the US population has diabetes mellitus (DM), and that 27.8% of this population has undiagnosed DM. Patients with DM have twice the medical costs of those without DM, and the direct financial burden on the US healthcare system was $176 billion in 2012.

All individuals with type 1 DM (5% of the diabetic population) require insulin to control blood glucose levels; in addition, many individuals with type 2 DM require insulin as the disease progresses. Exogenous insulin is available in rapid-, short-, intermediate-, and long-acting formulations, and the goals of therapy are to mimic endogenous insulin while reducing the risk for adverse events and complications. New routes of administration, such as oral and buccal, and new fixed-dose combinations (with more than 1 insulin or an insulin component) are in development to improve and optimize diabetes management.

It is vital for clinicians who manage DM to have a thorough understanding of insulin therapy, including insulin physiology and its dysfunction seen in DM; an overview on current and emerging insulin therapies; and best practices on constructing insulin-based treatment regimens.

This interactive activity will provide information on insulin physiology in individuals without DM, the physiologic dysfunction of insulin seen in patients with DM, the differences between exogenous and endogenous administration of insulin, an overview on the current and emerging insulin therapies, and best practices for constructing insulin-based regimens for patients with DM.

LEARNING OBJECTIVES
Upon completion of this activity, participants should better be able to:

• Describe the current understanding of insulin physiology in patients without diabetes mellitus (DM)
• Recognize the pathophysiologic consequences of insulin dysfunction in patients with DM
• Compare and contrast the physiologic effects of exogenously and endogenously administered insulin
• Distinguish the similarities and variability among current and emerging insulin products
• Construct optimum insulin-based regimens for patients with DM

FACULTY
Janet B. McGill, MD, MA, FACE
Professor of Medicine
Washington University School of Medicine
Director of the Fellowship in Endocrinology, Diabetes and Metabolism
Attending Physician
Barnes-Jewish Hospital
St. Louis, Missouri
PHYSICIAN CONTINUING MEDICAL EDUCATION

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FEE
There is no fee to participate in this educational activity.
Data from the Centers for Disease Control and Prevention indicate that more than 29 million Americans (or 9.3% of the population) have diabetes mellitus (DM), and nearly 29% of those with diagnosed DM (aged 18 years or older) use insulin therapy for glucose management (Centers for Disease Control, 2014). A more recent analysis using National Health and Nutrition Examination Survey (NHANES) data estimates the prevalence of DM in 2011 to 2012 at 12% to 14% of the population, with higher rates among certain subpopulations (Menke et al, 2015). Researchers estimate that the incidence of new cases of diabetes may increase from approximately 8 cases per 1,000 (seen in 2008) to approximately 15 cases per 1,000 in 2050 (Boyle et al, 2010). Insulin therapy is considered the cornerstone of diabetes management. All patients with type 1 DM (T1DM) and many patients with type 2 DM (T2DM) require exogenous insulin. One of the main goals of insulin therapy is to mimic the physiology of endogenous insulin. This goal is challenging for many reasons. Exogenous insulin does reduce and improve glycemic indexes but can also be associated with hypoglycemia and weight gain.

Endocrinologists, primary care physicians, pharmacists, and other healthcare providers involved in the management of DM must understand insulin physiology and the differences between endogenous and exogenous insulin to better construct optimum insulin-based regimens and maximize patient outcomes and quality of life.

This CME-certified activity seeks to address these educational needs while bridging existing knowledge gaps to help improve the clinical outcomes of patients with DM.

**INSULIN PHYSIOLOGY IN INDIVIDUALS WITHOUT DM**

Insulin, a pancreatic hormone, regulates blood glucose levels through inhibitory and stimulatory actions. It inhibits glycogenolysis, gluconeogenesis, lipolysis, and proteolysis. The inhibition of hepatic glucose production is the principal action of insulin that affects blood glucose, whereas the stimulatory actions, promoting lipogenesis and cell uptake of glucose, have a limited role (Aronoff et al, 2004).

In healthy individuals, pancreatic beta cells secrete insulin in a pulsatile-like method in response to nutrient levels, especially glucose concentrations. During a meal, the release of insulin occurs in 2 phases (Meier et al, 2005; Newsholme et al, 2014). In the first phase, insulin is secreted within 5 to 10 minutes of increased blood glucose. This occurs as an initial burst. During the second phase, the beta cells release insulin more gradually, within 30 to 60 minutes of the blood glucose increase (Newsholme et al, 2014). Insulin maintains blood glucose concentration between 72 and 180 mg/dL (4-10 mmol/L), and peak insulin levels may range from 15 to 250 mU/L.

When insulin reaches the liver, it inhibits gluconeogenesis and glycogenolysis and stimulates glycogen synthesis, lipogenesis, glycolysis, and glucose uptake by the hepatocytes (Rui, 2014). In the periphery, cells take up glucose through membrane transporters referred to as glucose transporters (GLUT). Of 6 isomers, only GLUT-4 requires insulin to transport glucose into the cell. This is referred to as the insulin-sensitive glucose transporter. GLUT-4 is located in muscle and adipose tissue, and skeletal muscles account for approximately 75% “of whole-body insulin-stimulated glucose uptake” (Newsholme et al, 2014; Shulman et al, 1990). Although muscle and adipose tissue contain GLUT-4, they also contain other GLUT isomers. This allows for some uptake of glucose independently from insulin (Sonksen and Sonksen, 2000).

During the fasting state, glycogenolysis and gluconeogenesis in the liver supply the body with glucose, and insulin is released to maintain a glucose concentration of approximately 90 mg/dL (5 mmol/L) (Sonksen and Sonksen, 2000). A decrease in insulin concentration increases the release of glucagon and catecholamines and activates glycogen phosphory-
lase, which promotes glycogenolysis (Rui, 2014). At steady state, glucose production is matched with glucose clearance. The uptake of glucose by peripheral tissue determines the disposal of glucose. In the fasting state, the brain takes up approximately 50% of glucose from the blood, lean tissues use approximately 30%, and adipose tissue and red blood cells use the remaining 20% (Sonksen and Sonksen, 2000).

After prolonged fasting, insulin levels further decrease and the glycogen stores in the liver are depleted. The main mechanism for glucose production then becomes gluconeogenesis. Gluconeogenesis requires substrates obtained through lipolysis and proteolysis, which are promoted by a decrease in insulin concentration. The breakdown of lipids produces glycerol and free fatty acids, and the breakdown of proteins produces amino acids, both of which the liver can use for gluconeogenesis (Sonksen and Sonksen, 2000).

Ketogenesis is the process whereby ketone bodies are produced from free fatty acids and specific amino acid substrates. Ketone bodies can then be used as an energy source by muscle tissue and in a limited fashion by neural tissue. In contrast, red blood cells require glucose and cannot use ketones as an energy substrate. During prolonged fasting, ketone body concentration can increase up to approximately 126 mg/dL (7 mmol/L). In a normal fasting state, ketone body concentration remains near 1.8 mg/dL (0.1 mmol/L) (Sonksen and Sonksen, 2000).

**PHYSIOLOGIC DYSFUNCTION OF INSULIN SEEN IN DM**

T1DM and T2DM are characterized by fasting hyperglycemia. In T1DM, the beta cells are destroyed by autoimmune mechanisms and therefore insulin production is either markedly reduced or absent, whereas the pathophysiology of T2DM typically begins with insulin resistance and elevated insulin levels. As insulin secretory capacity begins to wane, post-prandial glucose levels increase followed by fasting hyperglycemia (Aronoff et al, 2004). The progression to fasting hyperglycemia occurs with increasing insulin resistance of the liver and peripheral tissue and progressive dysfunction of pancreatic beta cells.

In the absence of insulin or increased insulin resistance, the liver continuously produces glucose and the glucagon, cortisol, growth hormone, and catecholamine concentrations increase (Sonksen and Sonksen, 2000). Overssecretion of anti-insulin hormones amplifies the overproduction of glucose, and the blood glucose level continues to increase. In response to hyperglycemia, cellular uptake of glucose may increase, and the kidneys excrete glucose when the reabsorption threshold is met. This threshold is approximately 180 to 200 mg/dL (10-11 mmol/L) in patients without DM and is elevated in patients with DM (approximately 240 mg/dL [13 mmol/L]) (Wilding, 2014). Once that threshold is met, renal excretion of glucose increases with the increase of glucose. A dynamic steady state is reached when hepatic glucose production equals the renal excretion and tissue metabolism of glucose.

During prolonged hyperglycemia and severe insulin deficiency, escalated glycosuria results in an osmotic diuresis. Osmotic diuresis occurs when larger volumes of fluid are excreted due to high glucose concentrations filtered by the kidneys. This causes increased thirst, polyuria, and weight loss, and if not corrected, severe dehydration, hypotension, and electrolyte imbalances.

In addition to the overproduction of glucose, the lack of insulin also causes the overproduction of ketones. Without insulin, lipolysis and proteolysis continue unchecked, and free fatty acids and amino acids are delivered to the liver. The liver uses free fatty acids and amino acids as substrates for ketogenesis and releases ketone bodies into systemic circulation. Ketones are water and lipid soluble. Because of their solubility, they do not require transporters to cross the cell membrane, and often replace glucose for metabolism. Cell uptake of glucose decreases, and blood glucose levels can increase to markedly elevated levels (Sonksen and Sonksen, 2000).

For the disposal of ketones, metabolism is required. The kidneys do not have a ketone reabsorption threshold as they do with glucose; therefore, urine ketones are reflective of blood ketone levels. The concentration of ketones in the blood can increase to >360 mg/dL (>20 mmol/L), which leads to metabolic acidosis (Sonksen and Sonksen, 2000).
Ketone bodies are acidic, and after compensatory mechanisms (buffering with bicarbonate and hyper-ventilation) have been exhausted, their accumulation decreases the pH of blood to <7.3. Ketoacidosis typically occurs and can result in diabetic coma.

**DIFFERENCES BETWEEN ENDOGENOUS AND EXOGENOUS INSULIN ADMINISTRATION**

Exogenous insulin is the cornerstone treatment for DM. All patients with T1DM require insulin therapy, and many patients with T2DM often require insulin therapy as the disease progresses. Although exogenous insulin is structurally similar to endogenous insulin, it does not share similar in vivo kinetics. When pancreatic beta cells release endogenous insulin, insulin first enters the liver via the portal vein. The liver then removes approximately 80% of the insulin before it reaches the peripheral circulation; therefore, the liver receives the highest concentration of insulin (Meier et al, 2005).

Exogenous insulin is administered subcutaneously and does not go to the liver first. The peripheral circulation, not the liver, receives the highest dose of insulin. This causes the liver to be under-insulinized and the periphery to be over-insulinized. High doses of insulin in the periphery promote increased cell uptake of glucose, which can result in hypoglycemia. It also decreases peripheral lipolysis and increases peripheral lipogenesis, which can result in weight gain. In addition, exogenous insulin does not sufficiently suppress glucagon, which promotes further glycogenolysis and gluconeogenesis (Aronoff et al, 2004).

**OVERVIEW OF CURRENT AND EMERGING INSULINS**

Historically, insulin was derived from animals, and it lacked purity and often caused allergic reactions. Currently available insulin preparations are produced with recombinant DNA technology, which has reduced the frequency of allergic reactions and provides a purer product. Insulins are available in rapid-, short-, intermediate-, and long-acting formulations. The concentration of these agents is commonly 100 U/mL (U-100), although other concentrations are available. For example, regular human insulin is available at 500 U/mL (U-500), which is reserved for severe hyperglycemia cases, insulin glargine is available at 300 U/mL (U-300), and insulin lispro is available at a 200 U/mL (U-200) formulation (Kroon et al, 2010; Eli Lilly and Company Press Release, 2015).

Rapid-acting formulations are analogs of human insulin, and include insulin aspart, insulin lispro (which is also available in the higher 200 U/mL concentration), and insulin glulisine. The US Food and Drug Administration (FDA) has approved them for the use in insulin pumps, and they also are used for control of postprandial blood glucose (Kroon et al, 2010). As the name implies, rapid-acting formulations have the quickest onset of action, within 15 minutes for insulin aspart and insulin lispro and 15 to 30 minutes for insulin glulisine, and the shortest duration, approximately 3 to 5 hours (Galdo et al, 2014; Kroon et al, 2010). Peak concentration is observed at 30 minutes to 3 hours, depending on the agent. Because of the quick onset, rapid-acting analogs are administered up to 15 minutes before a meal. The ability to take these agents shortly before the start of a meal may improve patient adherence, and the pharmacodynamics of these agents are similar to the secretion of physiologic insulin. These characteristics reduce the risk for hypoglycemia. The rapid-acting analogs are considered to be similar in efficacy and safety (Siebenhofer et al, 2006).

Regular human insulin is considered a short-acting formulation, and like rapid-acting insulin, is used for the control of postprandial blood glucose (Kroon et al, 2010). It has an onset of 30 minutes to 1 hour, a peak of 2 to 4 hours, a duration of 5 to 8 hours, and is administered approximately 30 minutes before a meal, which may be inconvenient for patients (Galdo et al, 2014; Kroon et al, 2010). In addition, the delayed peak can increase the risk for hypoglycemia hours after a meal. Although adherence may be more difficult and hypoglycemic risk is increased, regular insulin may be beneficial in specific cases, such as before ingesting a fatty meal with high carbohydrates (Herbst and Hirsch, 2002).

A recent Cochrane Review concluded that short-acting insulin analogs had a minor benefit when compared to regular human insulin (Siebenhofer et al, 2006). In patients with TIDM, the study authors found
that the weighted mean difference of glycated hemoglobin (HbA1c) was -0.1% in favor of regular insulin and that the weighted mean difference of glycated hemoglobin has a slower redissolution rate than short-acting insulin analogs in patients with T1DM and T2DM. The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) prefer analogs instead of human insulin for diabetes management (Handelsman, et al, 2015; American Diabetes Association, 2015). Researchers have found that analogs have pharmacodynamic profiles more similar to endogenous insulin, reduced risk for hypoglycemia, and in some cases, improved glycemic control. There is some debate, however, on whether the benefits of analogs outweigh the higher cost of these agents (Davidson, 2014; Grunberger, 2014).

Neutral Protamine Hagedorn (NPH) is regular human insulin complexed with protamine (Kroon et al, 2010). This combination slows absorption and makes NPH an intermediate-acting formulation, with an onset of 1 to 2 hours, a peak of 4 to 10 hours, and duration that can exceed 14 hours (Galdo et al, 2014; Kroon et al, 2010). The amount of the NPH dose can alter pharmacodynamics; a larger dose may have a longer duration and delayed peak. NPH, as an intermediate formulation, is most commonly used for basal dosing.

Insulin detemir and insulin glargine, long-acting insulin analogs, are also used for basal dosing. Insulin detemir is coupled with a fatty acid that has a high affinity for albumin and delays absorption. This delay gives insulin detemir a flat peak at 6 to 8 hours, and duration of up to 20 to 24 hours (Galdo et al, 2014; Kroon et al, 2010). The absorption of insulin glargine is delayed because it has a pH of 4. When administered, insulin glargine forms microprecipitates in the tissue that slowly release insulin. The duration of insulin glargine is approximately 24 hours, and it is peakless (Galdo et al, 2014; Kroon et al, 2010). Because of these modifications, insulin detemir and insulin glargine should not be combined with other insulins in the same syringe for administration. Insulin detemir may be dosed twice daily if glycemic goals are not met, but the long-acting insulins are often dosed once daily at bedtime.

In February 2015, the FDA approved insulin glargine 300 U/mL (Sanofi Press Release, 2015a). This higher concentration has a slower redissolution rate than insulin glargine 100 U/mL. Slower redissolution prolongs absorption and further flattens peak concentration. During a 6-month study, researchers randomized 807 patients with T2DM receiving prandial insulin to receive insulin glargine 300 U/mL or 100 U/mL (Riddle et al, 2014). They found that insulin glargine 300 U/mL and 100 U/mL shared similar efficacy for the reduction of HbA1c. Patients receiving insulin glargine 300 U/mL experienced fewer episodes of nocturnal hypoglycemia than patients receiving 100 U/mL (36% vs 46%, respectively; \( P < .005 \)) (Riddle et al, 2014). Similar results were found in patients with T2DM receiving oral glucose-lowering drugs (Bolli et al, 2015; Yki-Järvinen et al, 2015).

When insulin glargine and insulin detemir have been compared, insulin detemir requires a higher daily dose but is also associated with less weight gain (Rosenstock et al, 2008; Swinnen et al, 2008). Both reduce HbA1c to a similar extent. In a 52-week study, researchers randomized 582 patients with T2DM to receive insulin detemir or insulin glargine (Rosenstock et al, 2008). Patients receiving insulin detemir gained 2.7 kg (5.9 lb) compared to 3.5 kg (7.7 lb) gained by patients receiving insulin glargine (intent-to-treat population, \( P = .03 \)). The mean daily dose of insulin detemir was 0.78 U/kg compared with 0.44 U/kg for insulin glargine (Rosenstock et al, 2008). Researchers evaluating 973 patients over 24 weeks found similar results. Insulin glargine was associated with an additional 0.77 kg (1.7 lb) weight gain (1.4 ± 3.2 kg \([3.1 ± 7.0 \text{ lb}]\) vs 0.6 ± 2.9 kg \([1.3 ± 6.4 \text{ lb}]\); \( P < .001 \)), and insulin detemir was associated with the use of an additional 33 units per day (43.5 ± 29.0 U vs 76.5 ± 50.5 U, \( P < .001 \)) (Swinnen et al, 2010).

Compared with NPH, insulin glargine and insulin detemir are associated with fewer cases of hypoglycemia, especially nocturnal hypoglycemia, and insulin detemir is associated with less weight gain (Hermansen et al, 2006; Rosenstock et al, 2005). In a meta-analysis, insulin glargine reduced the risk for severe hypoglycemia and severe nocturnal hypoglycemia by 46% \( (P = .0442) \) and 59% \( (P = .0231) \), respectively, compared with NPH (Rosenstock et al, 2005). During a 24-week period, insulin detemir reduced the risk for “all hypoglycemia” and nocturnal hypoglycemia by 47% and 55%, respectively, compared with NPH \( (P < .001 \text{ for both comparisons}) \) (Hermansen et al,
In the same study, researchers also found that insulin detemir was associated with a mean weight gain of 1.2 kg (2.6 lb) compared with a mean weight gain with NPH of 2.8 kg (6.2 lb) ($P < .001$).

Insulin formulations also are available that include premixtures of different types of insulins: NPH with regular human insulin (70/30), lispro protamine with lispro (50/50 and 75/25), and aspart protamine with aspart (70/30) (Kroon et al, 2010). Premixtures offer biphasic pharmacodynamics, which reduces the number of injections. This can translate into improved patient adherence compared with prandial and basal-bolus dosing but does not offer ideal physiological pharmacodynamics. Overall, premixtures are associated with increased hypoglycemia and weight gain when compared with basal dosing (Holman et al, 2009).

In February 2015, an inhaled insulin formulation was re-introduced (Sanofi Press Release, 2015b). A previously available formulation of inhaled insulin was removed from the market in 2007 due to poor patient/clinician acceptance of the drug (Mack, 2007). Inhaled insulin is classified as rapid acting and is taken before meals (Afrezza prescribing information, 2015). Peak insulin concentration occurs within 12 to 15 minutes after administration, and maximum effect occurred at approximately 50 minutes after administration. Like other insulins, hypoglycemia is a common adverse event. Coughing was also identified as a common side effect. Inhaled insulin may be beneficial to reduce the number of injections for patients with severe fear of needles.

In addition to the myriad insulin formations that have been approved for use, there also are numerous agents in development and a couple that have just been recently approved by the FDA. Insulin degludec was approved for use by the FDA in September 2015 and will be available at 2 different concentrations: 100 U/mL and 200 U/mL. A combination product of insulin aspart and insulin degludec also was recently approved by the FDA. Insulin degludec, an ultra–long-acting insulin, is coupled with a fatty di-acid. When administered, degludec forms multihexamer assemblies that slow absorption. This results in a peakless pharmacodynamics profile with a duration of >40 hours. The pharmacodynamic profile allows variation of dosing without affecting glycemic control and safety. The ability to vary dosing schedules may improve patient adherence (Meneghini et al, 2013). Insulin degludec also is associated with reduced risk for nocturnal hypoglycemia when compared with other long-acting insulins (Hirsch et al, 2012; Zinman et al, 2012).

Other emerging agents include injectables as well as other routes of administration. Injections of current interest include pegylated lispro and ultra–rapid-acting insulin analogs. Pegylated lispro is in phase 3 studies and is being evaluated for use as a basal insulin. Researchers presented data for pegylated lispro at the ADA Scientific Session in June 2015. Abstracts from the conference suggest that pegylated lispro is associated with better glycemic control, reduced nocturnal hypoglycemia, and less weight gain compared with insulin glargine (Davies et al, 2015) and that it has hepato-preferential action (Mudaliar et al, 2015). The development of ultra–rapid-acting insulin has also accelerated. For the development of faster-acting insulin aspart, researchers included nicotinamide as an excipient to the formulation to increase the rate of absorption and shorten the time to onset (Buckley et al, 2015). In March 2015, phase 3a trials for faster-acting aspart reached completion (Novo Nordisk Company Announcement, 2015). Abstracts presented at the ADA Scientific Session in 2015 suggest that faster-acting aspart has an earlier onset and greater glucose-lowering effect than aspart (Heise et al, 2015).

Fixed-dose combinations of insulins and other antidiabetic agents are also emerging, including a combination of insulin degludec and liraglutide (which is approved in the European Union and Switzerland, and was recently submitted to the FDA for approval) and a fixed-dose combination of insulin degludec and lixisenatide (currently in phase 3 development).

Other administration routes of interest include oral, buccal, and transdermal (Sanlioglu et al, 2013). Oral insulin is ideal in concept, but difficult to formulate. It maintains hepatic first-pass metabolism, similar to endogenous insulin, but passing through the gastrointestinal tract without degradation is difficult to achieve. Many companies have oral insulins in development. Buccal spray has shown prandial benefits with an onset of 30 minutes
and duration <2 hours. Hypoglycemia risk is reduced with the short onset and duration.

**DELIVERY SYSTEMS**

Available insulin formulations are mainly delivered through subcutaneous administration. Subcutaneous administration is achieved with syringes, prefilled pens, and insulin pumps. Syringes allow patients to free-mix insulin, which can reduce the number of injections, whereas pens offer convenience for portability, accuracy, and ease for patients with dexterity and visual impairment. Only regular insulin is used for intravenous administration, and intravenous administration is reserved for inpatient use.

Independent of pen or syringe use, injection site is important for appropriate administration. Most exogenous insulins can be injected in the abdomen, deltoids, gluteus, and thighs. Absorption of insulin can vary per site due to differences in blood flow; therefore, the injection site should remain consistent. The abdomen has quickest absorption followed by deltoids, thighs, and gluteus. Although the injection site should remain constant, the injection should be administered in different areas within the site to avoid lipohypertrophy. Absorption rates can also be altered with exercise, rubbing or massaging, and increased temperature of the injection site.

An insulin pump can be used to deliver rapid-acting insulin and can be beneficial for controlling blood glucose, especially in patients with T1DM receiving intensive insulin therapy (American Diabetes Association, 2004a; Cummins et al, 2010). Pumps mimic physiologic insulin with basal-bolus dosing and may help reduce hypoglycemia. They can also offer greater lifestyle flexibility, especially related to meals and travel. Insulin pumps are available as traditional and patch pumps. Patch pumps differ from traditional pumps in that they adhere to the body, do not have tubing, and tend to be smaller. Patients can adjust doses using a wireless controller (Anhalt et al, 2010). Patients selecting an insulin pump should have strong self-motivation and self-management skills and knowledge of carbohydrate counting. In a meta-analysis, researchers found that patients with T1DM receiving continuous subcutaneous insulin infusion had lower HbA1c levels, reduced variability of glucose concentrations, and an average reduction of 14% in insulin dose compared to patients receiving multiple daily injections (Pickup et al, 2002).

**GOALS OF INSULIN THERAPY**

Although exogenous insulin acts differently from endogenous insulin, the main goal of insulin therapy is to mimic the endogenous insulin physiology. Treatment goals provided by the ADA and the AACE can help achieve this (Handelsman et al, 2015; American Diabetes Association, 2015). Both associations suggest specific glycemic targets but also support individualization when appropriate. The ADA suggests an HbA1c <7%, fasting glucose 80 to 130 mg/dL, and a postprandial glucose <180 mg/dL. The HbA1c should be monitored ≥2 times/year in patients with stable values and ≥4 times/year in patients with changing therapy or unstable values. The AACE suggests lower glycemic targets than the ADA: HbA1c <6.5%, fasting glucose <110 mg/dL, and postprandial <140 mg/dL.

Both groups support less stringent goals for patients at high risk for hypoglycemia, a short life expectancy, a longer duration of disease, vascular complications, and/or comorbidities (Handelsman et al, 2015; American Diabetes Association, 2015).

Along with glycemic targets, treatment goals should include the avoidance of adverse events, such as hypoglycemia and weight gain, and the prevention of micro- and macrovascular complications (American Diabetes Association, 2015). Patients should have blood pressure, kidney function, and lipid levels monitored, and should be screened for retinopathy, diabetic peripheral neuropathy, and have routine foot care.

**CONSTRUCTING INSULIN-BASED REGIMENS FOR PATIENTS WITH DM**

Insulin regimens vary between T1DM and T2DM. Physiologic insulin replacement, also known as basal-bolus dosing, is considered the most effective insulin regimen for glycemic control in patients with T1DM (Handelsman et al, 2015; American Diabetes Association, 2015). With this regimen, insulin administration mimics endogenous insulin as closely as possible. Insulin can be administered with multiple daily injections or continuous subcutaneous insulin infusion. The ADA and AACE
prefer the use of insulin analogs for the management of T1DM because they are associated with less risk for hypoglycemia than regular human insulin and NPH.

For T1DM, initial insulin daily dose is calculated as 0.4 to 0.5 U/kg/day, and 40% to 50% of that daily dose is allocated to basal insulin (Handelsman et al, 2015). A total of 10% to 20% of insulin is then allocated for each meal. Ideally, prandial dosing is determined based on premeal glucose and carbohydrate intake. Patients should be educated on carbohydrate counting. For patients who are very insulin sensitive, the insulin-to-carbohydrate ratio is often high, 1 U:20 g or more. For insulin-resistant disease, insulin-to-carbohydrate ratio can go down 1 U/3g. To determine individual insulin sensitivity, 1,800 can be divided by total daily dose, which equals the number of milligrams per deciliter of glucose reduced by 1 U of insulin (Handelsman et al, 2015).

If postprandial targets are not met, pramlintide, an injectable amylin analog, is an agent other than insulin approved for the use in adults with T1DM. Pramlintide does not replace insulin as a therapy, but it can be administered directly before major meals with prandial insulin. When initiating pramlintide, mealtime insulin should be decreased by 50% to reduce risk for hypoglycemia (Symlinpen, 2014). This includes the decrease of premixed insulin if used, and dose titrations should be separated by 3 days to prevent nausea from developing. Pramlintide delays gastric emptying, reduces secretion of glucagon, and improves satiety. Benefits include weight loss and decrease in insulin dose.

Management of T2DM often follows a step-up approach for therapy, and insulin therapy is often indicated with disease progression (Handelsman et al, 2015; American Diabetes Association, 2015). When first presenting, patients should receive metformin, unless contraindicated or not tolerated. If glycemic targets are not met, a second agent should be added. In this case, basal insulin is an appropriate option. The ADA suggests a starting dose of 10 U or 0.1 to 0.2 U/kg, and although NPH and regular insulin cost less, the ADA and AACE suggest insulin analogs for their preferred pharmacodynamics and reduced risk for hypoglycemia. Initial therapy with insulin may also be appropriate in patients with newly diagnosed DM and severe hyperglycemia (HbA1c ≥9% and fasting glucose ≥300 mg/dL) or symptomatic hyperglycemia.

To reach glycemic targets, insulin should be adjusted by 10% to 15%, or in 2 to 4 U increments, once or twice weekly (American Diabetes Association, 2015). If fasting blood glucose has not reached target or daily insulin dose is >0.5 U/kg/day, prandial insulin should be added before the largest meal or twice-daily premixed insulin should replace basal insulin. Pre-mealtime insulin should be dosed as 4 U, 0.1 U/kg, or as 10% of basal dose. Premixed insulin should initially be dosed with two-thirds of the current basal dose administered in the morning and one-third at night, or one-half in the morning and one-half at night. A trial with a glucagon-like peptide-1 receptor agonist may also be appropriate at this stage instead of adding prandial insulin. The next step for therapy escalation is basal-bolus dosing.

With T2DM, insulin is often combined with other antihyperglycemic medications. Sulfonylureas, meglitinides, and pramlintide are associated with hypoglycemia and when combined with insulin, the risk for hypoglycemia is increased. If hypoglycemia occurs, the cause should be addressed, and insulin dose can be reduced by 10% to 20%, or 4 U. Patients receiving intensive insulin therapy should be self-monitoring blood glucose to assess for hypoglycemia and insulin efficacy. The ADA suggests that blood glucose testing be completed ideally before meals, at bedtime, before exercise, during and after low blood glucose, and occasionally after meals (American Diabetes Association, 2015). This testing frequency can add up to 6 to 10 times per day. It is unclear whether testing is beneficial for patients with T2DM receiving oral agents.

PUTTING THEORY INTO PRACTICE: CASE-BASED APPLICATION

The following cases are constructed to provide insight into constructing optimal insulin-based regimens.

**Case 1**

MH is a 26-year-old woman with TIDM. TIDM was diagnosed when she was 13 years old, and she began multiple daily injections with basal-bolus insulin. Her blood glucose targets had been met previously.
Now she reports that she has had difficulty controlling her glucose levels during this past year. She is currently enrolled in graduate school and her schedule is varied. During the previous 3 months, she has increased her basal and prandial insulin doses.

Her most recent lab values are: HbA1c 8.1%; fasting glucose, 133 mg/dL; and average postprandial glucose, 194 mg/dL. MH reports having hypoglycemic reactions 2 to 5 days/week at different times. She does disclose that her food choices are not optimal, and due to social constraints, she often injects her insulin after eating. MH has gained weight and is generally unhappy with her overall glucose control. She is afraid to exercise because of unpredictable low glucose levels.

**Important points for the healthcare provider:**

The greater variability in glucose levels seen in this patient could be due to lifestyle, stress, and/or loss of C-peptide. With both high and low glucose levels in evidence, it is time to re-evaluate her treatment plan and explore other options for her diabetes management. An insulin pump would provide greater flexibility with dosing, is more discrete, and would allow the basal rate to be adjusted for different activity levels throughout the day. It would also allow the insulin infusion to be temporarily reduced or suspended for exercise. A pump and continuous glucose sensor combination would permit the greatest safety and fine-tuning of insulin doses. For patients who want to lose weight, adding pramlintide to either pre-meal injections or pump doses can reduce the insulin requirement at meals and curb appetite. Diabetes educators are great facilitators when significant changes in therapy like these are needed, especially when those changes include new technology.

**Case 2**

GV is a 62-year-old man who presented 1 year ago with an HbA1c of 10.7% and he was diagnosed with T2DM. Metformin with basal insulin was initiated at that time. After multiple titration steps, his insulin dose was 52 U and his HbA1c was 7.2%. He has gained 2.5 kg (5.5 lb) and has occasional low glucose levels with activity.

GV asks if other therapies are available to manage his diabetes. After a discussion about his goals of therapy, which include weight loss and no hypoglycemia, a long-acting glucagon-like peptide-1 receptor agonist is started. You also referred GV to a dietitian to discuss calorie reduction.

GV’s basal insulin dose was dropped by 30% initially, then was further reduced as he progressed with his dietary changes and began walking 2 miles daily. A sodium-glucose transporter-2 (SGLT-2) inhibitor was added, and his insulin dose was reduced further. His insulin was discontinued when the dose reached <0.15 U/kg, and he monitored his glucose closely. After 6 months of down-titration of insulin and replacement with other agents, his weight decreased by 6.4 kg (14 lb) and his HbA1c was 6.4%. GV is happy with these results and intends to continue the diet and increase his exercise now that hypoglycemia is not a concern.

**Important points for the healthcare provider:**

This case illustrates the importance of reducing glucose toxicity while correcting dietary misadventures. For this type of patient, providers should not be afraid to use insulin as an initial therapy. Once the patient has made improvements in his dietary habits and his HbA1c levels have decreased, it is possible to add other antidiabetic therapies and move away from insulin to achieve the composite goals of therapy, such as weight loss and healthier lifestyle. Providers must also recognize that patients have their own goals for therapy, which are not always related to lowering HbA1c. This management strategy works the best in patients with a recent diagnosis of DM.

**Case 3**

TP is a 52-year-old woman with a 20-year history of T2DM. She was started on metformin at the time of her diagnosis, but due to persistent hyperglycemia, a sulfonylurea was added after 6 months. Her HbA1c remained >8%, so insulin was initiated at year 3. Diabetes education was not available at the time, so her basal insulin dose was titrated up to over 0.8 U/kg. TP claimed to monitor her blood glucose once daily but did not bring records to office visits. Her HbA1c finally
dropped to 7.8% on high doses of insulin plus metformin and a sulfonylurea, and remained near the target, but was suboptimal for several years. TP reports that during the past month, she has been waking up with a headache and damp from sweat. She also has these symptoms occasionally during the day. Her HbA1c is lower at 7.4%, which she states is from her efforts to lose weight.

You discuss management options with TP, which are likely limited by her duration of disease and need for insulin therapy. You refer her to see a diabetes educator (who is now available) and the educator instructs her in carbohydrate counting and prandial insulin dose adjustments. The sulfonylurea is stopped, her basal dose reduced to 0.4 U/kg, and prandial insulin is started at 1 U/6 g carbohydrate. She is allowed to adjust her prandial insulin by her carbohydrate intake and by her anticipated activity and she is instructed to test her glucose 4 times daily, and to bring her log to every visit for review.

At this most recent follow up her HbA1c is 7.4%, and her nighttime sweats are gone. At this point, you mention the use of a patch pump, which will deliver 30 U of basal insulin and up to 46 U of bolus insulin each day. She is anxious to avoid injections and have greater flexibility in her mealtimes. She agrees to use the patch pump.

After starting the patch pump, her HbA1c is 6.9%, and she admits to not giving bolus doses by injection for snacks, and missing occasional doses. These problems have been greatly reduced by the availability of insulin in a pump.

Important points for the healthcare provider:

This patient is both insulin resistant and insulin deficient. Since the initiation of basal insulin to oral antidiabetic agents often is the starting point for insulin treatment, there is a tendency to “over basal-ize.” This leads to risk for nighttime hypoglycemia and other low glucose levels throughout the day. The combination of insulin plus sulfonylureas aggravates this problem. This patient needs an adjustable insulin regimen and help/education to increase her skill levels regarding carbohydrate counting, testing her blood glucose levels, and making good food choices. Once these things are in place, patients generally appreciate your willingness to help them with the daily hassles that they encounter, such as recommending the use of a simple patch pump. Again, diabetes educators are great facilitators when changes in therapy are needed, especially when those changes include new technology. Finally, it is important to note that metformin should be continued in this scenario.

CLAIM CERTIFICATE

To receive acknowledgment of participation in this CME-certified activity, you must complete the evaluation and posttest.

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REFERENCES


Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015;17:386-394.


Davidson M. Insulin analogs—is there a compelling case to use them? No! Diabetes Care 2014;37:1771-1774.


Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care* 2014;37:2755-2762.


Wilding JPH. The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. *Metabolism* 2014;63:1228-1237.


**GLOSSARY OF PHARMACEUTICAL AGENTS**

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<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Degludec/liraglutide (fixed-dose combination)</td>
<td>N/A*</td>
</tr>
<tr>
<td>Degludec/lixisenatide (fixed-dose combination)</td>
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<td>Insulin (inhaled)</td>
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*Not approved for use in the United States as of the release date of this activity; development status of this agent is subject to change.*
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