REPORT

Introduction to Basal Insulin Therapy: Clinical Management of Diabetes

Jasmine D. Gonzalvo, PharmD, BCPS, BC-ADM, CDE, LDE

ABSTRACT

Diabetes is a series of metabolic conditions associated with many serious comorbidities, such as heart disease and stroke, peripheral arterial disease and lower-extremity amputations, retinopathy, nephropathy, and peripheral neuropathy. The American Diabetes Association, the American Association of Clinical Endocrinologists, and the International Diabetes Federation recommend that individuals with diabetes be as near to normoglycemic as possible. There are many glycemic management barriers among patients, such as cost, patient perceptions, and clinical inertia. Advancements in the treatment of diabetes with novel pharmacotherapeutic products have changed the therapeutic landscape of diabetes. Newer longer-acting insulin products that closely resemble endogenous insulin secretion patterns are demonstrating some improvements in clinical outcomes.

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For author information and disclosures, see end of text.

A staggering 30.3 million people in the United States (9.4%) are living with diabetes.[1] A recent report from the International Diabetes Federation (IDF) predicted that by 2045, more than 35 million Americans would have diabetes.[2,3] An estimated 1.5 million new cases were reported in 2015, but it is highly likely that many people with type 2 diabetes (T2D), formerly known as adult-onset diabetes, or noninsulin-dependent diabetes, go underreported or are unaware they have the disease.[1] An estimated 84 million adults—about 33.9%—have prediabetes, based on results of their fasting glucose and glycated hemoglobin levels (A1C).[1] What is concerning is that almost 90% of people with prediabetes are unaware of the condition.[4] The United States has the highest number of people with diagnosed and undiagnosed diabetes in the world.[2] Among those diagnosed, 90% to 95% have T2D, and 5% to 10% have type 1 diabetes (T1D).[1] About 2% to 10% of pregnancies are affected by gestational diabetes in the United States annually.[5] Along with its associated complications, such as cardiovascular disease, blindness, kidney disease, neuropathy, and lower-extremity amputation, diabetes places a substantial economic burden on the American healthcare system.[6]

Diabetes is considered to be a series of metabolic conditions associated with high rates of morbidity and mortality; it has been reported as the seventh leading cause of death in the United States.[1,6,7] The increasing prevalence of diabetes is a serious health crisis, impacting quality of life, overall health status, direct and indirect healthcare costs, and psychosocial factors.[6,8] Based on recent data (2017) collected and reported by the IDF, 176,740 deaths in the United States were related to diabetes.[2]

The escalating rates of prediabetes among adults 18 years or older in the United States are astounding.[1] Based on published data from the National Diabetes Statistics Report, 84.1 million people had prediabetes in 2015, and nearly half of those were 65 years or older.[1] As the population ages and the rates of obesity increase, the incidence of diabetes is expected to rise.[6] Correspondingly, the economic burden of diabetes will significantly increase among the elderly population, according to the IDF report.[2]

TABLE 1. Diagnostic Tests for Diabetes[7]

Criteria	Value
A1C	≥6.5%
Fasting plasma glucose	≥126 mg/dL (7.0 mmol/L)
2-hour glucose tolerance test	≥200 mg/dL (11.1 mmol/L)

A1c indicates glycated hemoglobin.

TABLE 2. Select Subtypes of Diabetes[6,12-15]

Subtype	Clinical Features
Maturity-onset diabetes of the young	• Heterogeneous group of disorders caused by genetic defect and autosomal dominant inheritance • Type 2 diabetes–like condition occurring in 2 or more previous generations with onset before 25 years and nonobese • Beta-cell dysfunction
Latent autoimmune diabetes in adults	• Type 2 diabetic phenotype with islet antibodies • Slow and progressive beta-cell failure
Iatrogenic	• Insulin-resistant diabetes commonly seen in patients with thalassemia • Directly proportional to the number of transfusions and age
Glucocorticoid-induced diabetes	• Complication of extended glucocorticoid use • Glucocorticoids exacerbate hyperglycemia

Childhood obesity and T2D among children and adolescents are rising at alarming rates.[6] An estimated 193,000 American children have diabetes and, of those, T1D accounts for approximately 169,000 cases.[1,2] Children with T2D are at increased risk of developing associated disease complications by the time they reach adulthood, although efforts can be implemented to prevent or delay the onset of diabetes.[2,9]

Compared with white individuals, racial minorities are more likely to have higher rates of diabetes and disease-related complications.[10] Although there is a higher prevalence of T1D among white children, minority children (10-19 years) are more frequently diagnosed with T2D.[1]

Pathophysiology of Diabetes

Elevated blood glucose concentrations are the result of the body's inability to produce insulin or its resistance to the action of insulin, or both. Complications often arise due to years of significant hyperglycemia.[6,8,11] A diagnosis of diabetes can be made based on A1C values or plasma glucose levels—either fasting blood glucose (FBG), or following an oral 2-hour glucose tolerance test (2-h PG) (**Table 1**).[7]

Although the diagnoses of people with diabetes are commonly categorized as type 1, type 2, or gestational, there are a variety of less-prevalent subtypes that have been recognized in recent years: maturity-onset diabetes of the young, latent autoimmune diabetes in adults, iatrogenic, and glucocorticoid-induced are a few select examples (**Table 2**).[6,12-15]

Type 1 Diabetes

Although known to be caused in some cases by an autoimmune response, resulting in pancreatic beta-cell destruction and impaired insulin production, some forms of T1D have no known etiologies.[6,7] While clinical presentation can vary and diagnosis can be challenging, symptoms of polyuria, polydipsia, and diabetic ketoacidosis are hallmark signs of T1D.[7] The American Diabetes Association (ADA) outlines 3 distinct stages of T1D, from presymptomatic (stage 1) through symptomatic hyperglycemia (stage 3). No strategies to prevent T1D are known.[7] Some risk factors include family history, race, and childhood viral infections.[7]

Type 2 Diabetes

T2D occurs when peripheral tissues, such as muscle and adipose tissue, become progressively resistant to insulin action, and the pancreas is unable to produce enough insulin to overcome resistance.[7] Many risk factors for T2D are modifiable including obesity, physical inactivity, poor nutrition, hypertension, smoking, and alcohol abuse.[7] However, age, race, low birth weight, gestational diabetes, and family history are examples of nonmodifiable risk factors.[7]

Gestational Diabetes

Some women who become glucose-intolerant during pregnancy develop gestational diabetes.[7] Common risk factors include obesity, gestational diabetes in a previous pregnancy, and having a family history of diabetes.[7] Hyperglycemia can result in negative maternal, fetal, and neonatal outcomes, particularly late in the second trimester.[7]

Diabetes Due to Other Causes

Some factors can precipitate diabetes, such as diseases of the pancreas and specific genetic defects in beta-cell function and insulin action.[7] Other causes can include select medications, such as those used in the treatment of HIV/AIDS or organ transplant.[7]

Complications of Diabetes

Poor glucose management can lead to life-threatening events and hospitalizations.[12] The effects of prolonged hyperglycemia, insulin resistance, excessive endogenous levels of insulin, and obesity negatively impact different organ systems in the body (**Table 3**).[6] Data collected as of 2010 from the National Hospital Discharge Survey revealed that more than 5 million hospital admissions in the United States were associated with patients with diabetes.[13] Another extensive cohort study reported that severe complications, such as myocardial infarction, are likely to occur in individuals with T2D.[14]

Heart Disease and Stroke

Cardiovascular (CV) disease accounts for about 65% of all deaths in people with diabetes.[6] In fact, people with diabetes have 2 to 4 times greater risk of death due to heart disease, according to Deshpande et al.[6] Hypertension is common among patients with T2D, placing them at higher risk for CV and renal diseases.[15] Investigators of the United Kingdom Prospective Diabetes Study Group (UKPDS) revealed that maintaining tight control of blood pressure in patients with T2D significantly reduced the risk of fatal CV events, retinopathy, and visual acuity.[15] While it has been established that diabetes is a significant risk factor for stroke, diabetes has also been linked to increased mortality and poor poststroke outcomes.[16] As demonstrated in the Lausanne Stroke Registry, people with diabetes are at greater risk for cerebral infarction or intracerebral hemorrhage with their first stroke.[16]

Peripheral Arterial Disease and Lower-Extremity Amputations

Diabetes and smoking are significant risk factors for peripheral arterial disease (PAD), which manifests itself as atherosclerotic occlusive disease and is associated with lower-extremity amputation.[17] It is well established that PAD can be asymptomatic in patients with diabetes; often, patients present too late, and amputation is necessary.[17] In an effort to avoid serious complications, people with diabetes are advised to inspect their feet daily for signs of injury or infection.[17]

Retinopathy

In the United States, diabetic retinopathy is responsible for the most new cases of blindness annually.[17] Signs of diabetic retinopathy may manifest after 5 years following the onset of hyperglycemia. In addition to length and severity of chronic hyperglycemia, other factors, such as diabetic renal disease, hypertension, and dyslipidemia, are associated with diabetic retinopathy. Optimal glucose management may prevent the development or progression to diabetic retinopathy.[17]

Nephropathy

In the United States, diabetic nephropathy is the leading cause of end-stage renal disease.[17] Signs of diabetic nephropathy can manifest at around 10 years of disease duration. Nephropathy is often referred to as the "silent disease," because symptoms do not commonly appear until the later stages of chronic kidney disease. Urine albumin-to-creatinine ratio and estimated glomerular filtration rate should be assessed regularly to determine the severity or progression of diabetic nephropathy.[17]

Peripheral Neuropathy

Symptoms of peripheral neuropathy may present after 5 years of significant hyperglycemia, although as many as 50% of people with diabetes may not experience symptoms and would be at an increased risk for injury and subsequent complications. Optimal glucose management is the only way to prevent progressive nerve damage. Pharmacologic treatment may help with symptoms of significant neuropathy. Baseline and annual assessments with a 10-gram monofilament and a 128-Hz tuning fork are useful to identify individuals at a high risk of injury, infection, and complications.[17]

TABLE 3. Prevalence of Diabetes-Related Complications Among Patients with Diabetes[6]

Diabetes-Related Complications	Percentage
Stroke	6.6%
Congestive heart failure	7.9%
Coronary heart disease	9.1%
Chest pain	9.5%
Myocardial infarction	9.8%
Eye damage	18.9%
Foot problems	22.9%
Chronic kidney disease	27.8%

Available Therapies and Challenges Associated With Insulin Use

Optimal glycemic management is the cornerstone of reducing the risk of serious complications associated with diabetes.[18] The ADA publishes annual Standards of Medical Care in Diabetes, which provide evidence-based clinical guidance to help optimize care for people with diabetes.[7] The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) also regularly publish updated approaches to the management of diabetes (**Table 4**).[19]

The ADA recommends an A1C goal of less than 7.0%, and target glucose levels 80 to 130 mg/dL (preprandial) and less than 180 mg/dL (postprandial).[7] AACE/ACE recommends patients achieve and maintain A1C less than 6.5%, preprandial glucose target less than or equal to 110 mg/dL, and peak postprandial glucose target less than or equal to 140 mg/dL.[19] Among clinicians, it is a well-accepted practice to set patient-specific glycemic goals that account for comorbid conditions, or lack thereof.[7,19]

Although most people with diabetes will need pharmacotherapy, patients should be encouraged to maintain healthy, active lifestyles at all stages of diabetes.[7] The decision to begin any therapy—oral, insulin, or other injectable—should be made jointly by the patient and provider with appropriate considerations of evidence-based recommendations. The ADA recommends initiating metformin as first-line treatment for T2D at diagnosis unless contraindications exist.[7] When considering add-on therapy to metformin, pharmacologic recommendations have recently changed to place preference on the medications shown to have CV benefits, such as empagliflozin or liraglutide.[7] Dipeptidyl peptidase-4 (DPP-4)

TABLE 4. Principles of the AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm[19]

1. Lifestyle management includes the entire diabetes team.
2. Advise weight loss in all patients with prediabetes or type 2 diabetes who are overweight or obese.
3. The A1c target must be individualized based on age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia, adverse consequences of hypoglycemia, patient motivation, and adherence.
4. Glycemic management targets include fasting and postprandial glucose.
5. The choice of therapies must be individualized on the basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.
6. Minimizing risk of hypoglycemia is a priority.
7. Reducing risk of weight gain is a priority.
8. Initial acquisition cost of medications is only part of the total cost of care, which includes monitoring requirements, risk of hypoglycemia, weight gain, etc.
9. The algorithm stratifies choice of therapies based on initial A1c.
10. Combination therapy is usually required and should involve agents with complementary actions.
11. Comprehensive management includes lipid and blood pressure therapies, and managing related comorbidities.
12. Treatment must be evaluated frequently until stable (eg, every 3 months), and then less often.
13. The therapeutic regimen should be as simple as possible to optimize adherence.
14. The algorithm includes every FDA-approved class of medications for diabetes.

A1c indicates glycated hemoglobn; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology.
Adapted from Garber AJ, Abrahamson MJ, Barzilay JI, et al. *Endocr Pract.* 2017;23(2):207-238.

inhibitors, sodium glucose co-transporter 2 (SGLT-2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists are among the newer, commonly used medication classes that have offered some advantages over sulfonylureas, alpha glucosidase inhibitors, meglitinides, and thiazolidinediones (TZDs) over the last decade.[7]

Although insulin therapy is the mainstay of treatment for patients with T1D, many patients with T2D may eventually require insulin therapy.[7] Basal insulin regimens are often dosed once daily and are commonly added to oral diabetes medication regimens that do not provide optimal glucose management.[7] The longer-acting basal analogs (U-300 glargine or degludec) may offer some advantages in comparison to U-100 glargine or detemir.[7]

Patient Reluctance

Although it is well established that optimal glycemic management delays or prevents serious diabetic complications, more than 50% of patients with T2D do not achieve their target A1C of less than 7.0%.[18] The ADA, AACE, and IDF recommend that patients with diabetes be as near to normoglycemic as possible.[3,7,19] While the use of insulin has typically been reserved for patients with worsening diabetes, studies suggest that early treatments with insulin therapy have long-term benefits. The UKPDS researchers demonstrated long-term beneficial CV effects of early intensive glycemic management, which may have included insulin, in a population newly diagnosed with T2D.[20] The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial evaluated insulin glargine in patients with early T2D or prediabetes.[21] Participants with prediabetes who received insulin glargine were 28% less likely to develop diabetes during the study period than those who received standard oral treatment. However, those who received insulin glargine also had higher rates of hypoglycemia and weight gain of about 1.6 kg in a 6-year period.[21]

Despite convincing evidence that insulin is safe and effective, many patients and physicians are reluctant to start insulin therapy.[22] Fear of injections, weight gain, and hypoglycemia may be contributing factors as to why uptake is not greater. Many healthcare providers and patients are worried about hypoglycemia and its consequences. According to the ADA, risk factors for insulin-induced hypoglycemia are endogenous insulin deficiency, a history of hypoglycemia, aggressive glycemic therapy, recent moderate or intensive exercise, sleep, and renal failure.[23]

Hypoglycemia can increase the risk of injury and death, although reports from the Diabetes Control and Complications Trial state that severe hypoglycemia and low A1C account for only 9% of hypoglycemic episodes.[24] The ADA estimates that 50% of all hypoglycemic events can be predicted by patients who self-monitor blood glucose levels.[23] Despite the evidence supporting the use of insulin in patients with T2D, previous reports suggest that insulin is used in less than 50% of patients for whom it is recommended.[25] Providing patient education on the signs, symptoms, and appropriate management of hypoglycemia, suggesting dietary and exercise modifications, making necessary medication adjustments, and monitoring blood glucoses frequently help to decrease the risk of hypoglycemia.[23]

Select Barriers to Use of Insulin Products

Some patients may not be able to afford some of the newer insulin products.[25] Many of the newer insulin analogs are more costly than older formulations (such as neutral protamine Hagedorn [NPH] or regular insulin).[25] Newer insulin products resemble endogenous insulin secretion patterns, and there are advantages to their use.[25] It has been reported that patients are reluctant to begin insulin therapy—basal or prandial—because they perceive insulin regimens as complicated and confusing.[25] To help patients understand how best to start or modify their insulin therapy, algorithms that provide a stepwise approach to basal–bolus insulin therapy and bolus dose adjustments are available.[26]

Basal, premixed, and basal-prandial insulin regimens using the newer insulin products are all designed to help patients safely achieve their glycemic goals, with the goal of attenuating adverse

effects, such as hypoglycemia and weight gain.[19] Long-acting insulins, such as U-100 insulin glargine, U-300 insulin glargine, insulin degludec, and insulin detemir, are insulin formulations with predictable pharmacokinetic and pharmacodynamic profiles.

Although weight gain is associated with insulin, results of a meta-analysis revealed that the combination of metformin with basal or basal–bolus insulin resulted in statistically significant reductions in weight gain compared with insulin monotherapy.[27] Results of other randomized controlled trials demonstrated that the use of metformin with either insulin glargine or insulin detemir resulted in less weight gain than with NPH insulin.[27] According to the results of the Treating To Target in Type 2 Diabetes trial, basal insulin detemir was associated with less weight gain than biphasic insulin aspart twice daily or prandial insulin aspart 3 times daily.[28] Moreover, basal insulin detemir sustained its weight advantage after 3 years.[28] Basal insulins have an extended rate of absorption and long duration of action, thereby minimizing the risk of hypoglycemia as compared with faster acting insulins.[27]

Clinical Inertia and Current Challenges in Diabetes Therapy Management

Despite substantial evidence from clinically based or well-established guidelines, some healthcare providers fail to initiate therapy for diabetes.[29] Clinical inertia is defined as recognizing a problem but failing to act, start, or intensify therapy when there is substantial evidence to initiate treatment.[29] Studies done in the United States, Canada, and Europe confirm that clinical inertia among healthcare providers is widespread, at 30% to 68%.[29,30] A more recent study found clinical inertia rates to be as high as 57% among family physicians treating patients with diabetes; investigators reported poor glycemic control among those patients.[31] Many providers exhibit clinical inertia when they do not initiate more aggressive therapy for their patients who are not reaching targeted A1C concentrations because of assumptions of nonadherence to pharmacotherapy, diet, and exercise.[29]

Clinical inertia can also be seen in patients who are reluctant to begin, modify, or intensify therapy because of previously experienced adverse effects, perceived risks of treatments, or the notion that there is no need to be proactive when there are no apparent symptoms of disease.[29] Despite the results of less-than-optimal glucose levels, many prescribers do not advance a patient's therapy based on perceptions that glycemic values were improving.[29] Based on the results of a study examining changes in the "process" of diabetes management, patients achieved a significant reduction in A1C when clinicians intensified therapy based on protocol, which demonstrates that clinical inertia can be overcome.[29]

While guidelines for the management of diabetes are well established, clinical inertia is a barrier to improved patient outcomes. Better management of diabetes will require modification of current educational practices of providers and medical students.[29] Several approaches to reversing clinical inertia have been recommended, including medical education programs, emphasizing the significance of medical education about dangers of clinical inertia to undergraduate and graduate students, systemic self-assessments, and regular interactions with peers or opinion leaders.[32]

Newer Insulin Formulations

Insulin degludec, available in 100 units/mL (U-100) and 200 (U-200) units/mL, is a once-daily injection that is characterized by its long duration of action of more than 42 hours and half-life greater than 24 hours.[33] U-100 and U-200 are bioequivalent, but U-200 delivers half the volume of the U-100 formulation and allows for administration of up to 160 units in 1 dose.[33] Based on the results of a phase 3 clinical trial (BEGIN, a 1-year, randomized, treat-to-target trial), insulin degludec U-100 and U-200 proved noninferior to older basal insulins in patients with T1D and T2D.[33] Lower rates of severe hypoglycemia were also seen in participants receiving insulin degludec.[33]

There are 2 insulin glargine U-100 products (Basaglar, Lantus) which are biologically similar each other, indicating that it has no clinically meaningful differences in terms of safety, purity, and potency (ie, safety and effectiveness).[34] Insulin glargine injection 100 units/mL (Basaglar) is a long-acting, once-daily basal insulin that is approved for the treatment of T1D and T2D in adults and pediatric patients.[35] Based on a 24-week, phase 3 clinical trial consisting of 756 adult patients with T2D, a new biologically similar formulation of insulin glargine injection 100 units/mL (Basaglar) demonstrated noninferiority to a reference insulin glargine injection (Lantus).[36] Switching from insulin glargine 100 units/mL (Lantus) to insulin glargine 100 units/mL (Basaglar) is a 1:1 dose conversion.[35]

Another recently approved product is insulin glargine 300 units/mL, a long-acting basal insulin product that lasts for more than 24 hours and has proven to be as safe and effective as insulin glargine 100 units/mL. It has a longer duration of glucose-lowering action than insulin glargine 100 units/mL.[37] A series of multinational, open-label, parallel-group trials—known as EDITION I, II, III, and IV—led to the approval of insulin glargine 300 units/mL.[37-39] Insulin glargine 300 units/mL is as effective as insulin glargine 100 units/mL in reaching optimal A1C and fasting plasma glucose (FPG) levels in patients with T1D and T2D with less risk of nocturnal or severe hypoglycemia at any time of the day.[40] The TAKE CONTROL trial—patient-driven dose titration—enrolled participants with uncontrolled T2D into a 2-arm parallel-group, multicenter, multinational study.[40] Despite having to increase doses of insulin glargine 300 U/mL, more than doses of insulin glargine U-100/mL, patient-driven titration of insulin glargine 300 U/mL led to similar glycemic management in participants with T2D with a lower risk of nocturnal hypoglycemia.[37-39]

Combination products of basal insulins with GLP-1 receptor agonists are also newly approved, including insulin degludec/liraglutide and insulin glargine/lixisenatide. These medications are administered once daily. Both combination products have demonstrated weight loss in patients as compared with weight gain with insulin treatment alone. Trials have also demonstrated lower rates of hypoglycemia as compared with insulin monotherapy.[40,41]

Conclusions

Diabetes is a complex and serious illness that affects the lives of millions of people in the United States and worldwide.[5] Many dangerous complications often arise due to years of significant hyperglycemia that eventually causes harm to different organ systems in the body.[15] Diabetes is associated with high rates of morbidity and mortality, and it is reported to be the seventh leading cause of death in the United States.[4] The prevalence of diabetes is on the rise and is considered a serious health crisis that impacts a person's overall health status and quality of life, and is a burden to the US healthcare system.[8] Stringent glycemic management is the cornerstone for preventing the myriad of complications that can arise from diabetes and is strongly recommended by both the ADA and AACE.[2,3] Although most people with T2D will start oral antidiabetic agents initially, eventually many will require insulin therapy.[3] Innovative, longer-acting insulin products that closely resemble endogenous insulin secretion patterns are improving glycemic management in patients with diabetes.[37,42] ■

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Address correspondence to: jgonzalvo@purdue.edu.

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