Diabetes mellitus affects more than 26 million people in the United States,\textsuperscript{1} and the Centers for Disease Control and Prevention projects that more than 48 million people will have this disease in the United States by 2050.\textsuperscript{2} Diabetes mellitus is the leading cause of kidney failure, cardiovascular disease, nontraumatic lower-limb amputations, and new cases of blindness among U.S. adults.\textsuperscript{1} Despite numerous therapeutic options, glycemic control in the United States has not improved in recent years.\textsuperscript{3,4}
One of the reasons for this lack of metabolic control in patients with type 2 diabetes mellitus (T2DM) is a continued clinical inertia regarding treatment intensification and adjustment and an underuse of insulin in T2DM patients.\(^6\)

Poor glycemic control may be reflected in the failure of self-management by patients with diabetes mellitus, and inadequate intervention strategies by clinicians.\(^7\)-\(^11\) Attaining target glucose levels under various daily conditions—while avoiding hypoglycemia, dramatic excursions in blood glucose, and weight gain—can be difficult to achieve. Physicians need to overcome clinical inertia and intensify therapy in an appropriate and timely manner.\(^7\) Because T2DM is a progressive disease, many patients will ultimately need insulin therapy to achieve and maintain adequate glycemic control. Insulin remains essential treatment for patients with T2DM after oral therapy alone becomes inadequate.

The present article offers a case report to highlight the need for intensification and adjustment of insulin therapy in patients with T2DM. It also reviews factors that can impact achievement of treatment goals, challenges in adding medications to therapeutic regimens, and special challenges related to ethnic minorities and patient education.

Report of case
Sam is a 46-year-old Hispanic man who presented to his primary care physician for follow-up treatment for his T2DM. He went unwillingly but came at the urging of his wife who helped him realize that disease control is important for staying healthy. His experience with diabetes has not been good. He had vivid memories from early childhood of his grandmother receiving insulin injections from his mother. His grandmother lost her vision soon after starting insulin. She could not fill the syringe by herself and required help with her therapy.

As Sam aged, he remained slim and active. Nevertheless, diabetes mellitus still developed in Sam. Three years ago, when his glycosylated hemoglobin (HbA\(_{1c}\)) level was found to be 7.3%, he grudgingly agreed to begin self-monitoring of his blood glucose levels and to take metformin twice daily. Much to his surprise, his glucose control improved, and his HbA\(_{1c}\) level was 6.3%. A year later, despite following his nutritionist’s suggestions and exercising even more, Sam’s fasting plasma glucose level (FPG) level increased, and his HbA\(_{1c}\) level rose to 7.7%. He initially refused additional medications, but he later agreed to use glipizide (a sulfonylurea), noting that he preferred a medication that had been “tried and true” for many years and he did not want to take injections.

The addition of glipizide to Sam’s therapy worked only transiently. At the time of his follow-up to his primary care physician, he had not seen the doctor for 9 months because his FPG values had remained between 220 and 250 mg/dl and he did not want to know the next steps. He said he did not want to “take shots” and suffer as his grandmother had.

His physician was empathetic. Sam’s weight was stable and his body mass index was 24. His blood pressure was 118/76 mm Hg, despite
the fact that he was obviously upset at the time it was measured. His HbA1c level was 9.1%. As his phenotype was not typical for T2DM, and his treatment had little durability despite his significant lifestyle efforts the consideration for atypical types of diabetes was entertained. These patients may be the “thin diabetics” and often have family history of other autoimmune diseases. Nearly 10% of adults (>35 y/o) who think they have T2DM actually have a slowly progressive form of T1DM. Autoimmune antibodies (GAD65) were ordered as was the test for endogenous glucose production (c-peptide in conjunction with serum glucose). Alternatively, people from ethnic minorities, especially men of African descent can have a form of T2DM that is prone to go to diabetic ketoacidosis. This has been termed ketosis prone T2DM or “Flatbush diabetes”—named after a street in the Bronx in which this pattern was first described.

Islet-cell cytoplasm autoantibodies and glutamic acid decarboxylase autoantibodies (GADAs) can occur in patients with apparently typical T2DM. Data from the United Kingdom Prospective Diabetes Study 25, or UKPDS 2512 showed that among patients older than 45 years, the presence of GADAs was highly predictive of the likelihood of insulin requirements. In the ADOPT trial, 10% of the T2DM study population had GAD antibodies.13

The (GAD65) antibody was negative and his c-peptide was normal despite mild hyperglycemia (FSG 140 mg/dl).

Sam’s physician explained that in light of his significant hyperglycemia and the fact he has contributed so significantly to his control that insulin would be the safest and most effective therapy. The physician also explained that insulin has been a “tried and true” life-saving therapy for almost a century. Also as a hormone replacement it may have less side effects and drug interactions than most oral medications.

As a side note, if Sam were not slim and if he had a preponderance of postprandial hyperglycemia without an elevated fasting blood glucose level, then the short-acting glucagon-like peptide-1 (GLP-1) receptor agonist exenatide would be a treatment option. Because the longer-acting GLP-1 receptor agonists lower both fasting and postprandial blood glucose levels, they would also be options in this type of case, especially if weight loss is a consideration. However, because Sam was relatively slim with high FPG and HbA1c levels, insulin was his best option for therapeutic addition.

Sam was instructed regarding how to use an insulin pen, including the appropriate injection sites (ie, abdomen, outer arms, and thighs). See Figure 1. Upon placing the needle on the pen, he was shown how to do a 2-unit “air-shot” (ie, dialing up the pen to 2 units and ejecting a drop of insulin into the air to ensure that the injection would deliver the correct amount of insulin with no air bubbles). When administering the injection, he was advised to count to 6 to ensure that the full dose of insulin was delivered prior to withdrawing the needle from the injection site. The needle for the pen was short and 32 gauge. Sam was amazed how small and thin the needles were and was pleasantly surprised that he did not feel pain with the injection. Part of the education provided to Sam was to stress that the needle should be changed with each injection.

Sam began injecting 10 units of a basal insulin analog every night at bedtime. The PREDICTIVE 303 algorithm was given to Sam to enable him to self-titrerate his insulin (Table 1).14 He had always checked his fasting blood glucose levels daily and was amenable to being even more involved with his therapy, with the assurance that he would receive guidance from his physician. Increased self-monitoring of blood glucose levels gave him further feedback and a sense of empowerment. His fasting blood sugar (FBS) goal was between 80 and 130 mg/dL, which was individualized to his situation and which is a bit more lenient than...
the clinical trial goal of 80-110 mg/dL in the PREDICTIVE trial (see below for discussion of American Association of Clinical Endocrinologists and the American Diabetes Association guidelines). He was advised to increase the insulin dose by 3 units in his insulin dose every 3 days until his mean FBS was in that range. Sam was also told to continue using his oral diabetes medications (eg, sulfonylurea) but was advised to call his physician should he experience hypoglycemia. Any blood glucose level <80 mg/dL necessitated a reduction of 3 units in dose. However, if the total insulin dose exceeded 30 units, a 10% drop was recommended.

Sam returned 6 weeks later. He was found to have achieved his FBS goal with 36 units of insulin. He told his physician, “Shots aren’t bad after all.” At his next visit, 14 weeks after beginning insulin therapy, a repeat HbA1c measurement yielded a result of 6.9%.

Unfortunately, with the first ice storm of the winter Sam fell and broke his leg. Without his exercise routine, Sam’s FPG level began to rise. On the basis of guidance from the PREDICTIVE 303 algorithm, Sam added another 6 units of basal insulin to regain control over his FBS. After the cast was removed from his leg, his activity level increased and he was able to reduce the basal insulin dose to 36 units. Although Sam experienced many changes and challenges with his medications, he expressed confidence that he had the tools to control his diabetes mellitus as he had the flexibility to match his medication with his life circumstances.

Sam did well for the next 2 years. He then received a promotion at work, and his mealtimes became more erratic. He continued his exercise routine and followed his dietary recommendations, but he noted that his bedtime plasma glucose levels had risen to more than 200 mg/dL. He continued up-titration of the insulin dose to lower his evening glucose levels. The dose increased to 55 units of basal insulin. He began noting occasional morning (fasting) plasma glucose values of approximately 60 mg/dL. Most upsetting to him was that if his lunch was delayed because of his job, hypoglycemia would occur. He began carrying candy in his jacket for such occasions.

On Sam’s return to his physician, it was determined that the basal insulin dose was excessive. Sam agreed to add a second type of insulin, prandial or meal time insulin, to better cover his meal time insulin needs and to alleviate the hypoglycemia caused by excessive basal insulin and to allow him to regain control of his diabetes mellitus. The sulfonylurea was stopped. He was given a second pen with a rapid-acting insulin to take within 15 minutes of starting dinner, and he was asked to test his blood glucose levels before and 2 hours after dinner.

The starting dose of prandial insulin was 6 units. Instruction was given on how to titrate the dinner dose every 3 days by 1 unit—until his 2-hour postprandial glucose level was less than 180 mg/dL. If Sam were to eat a larger meal, perhaps at a restaurant, he would take an additional 2 units to compensate for the extra food. He would also continue during the next 3 days to titrate the basal insulin dose to achieve a FPG level between 80 and 130 mg/dL. The basal insulin dose was decreased to 45 units. Only 1 type of insulin was to be titrated on a given day.

After these adjustments in therapy, life quickly returned to normal for Sam. His hypoglycemia abated, and his glucose goals were achieved.

### Considerations for insulin therapy

Insulin should be considered for any patient undergoing triple therapy if his or her HbA1c levels are not at goal for more than a few (no more than 2 to 3) months. The AACE recommends insulin for patients with HbA1c levels >10%, regardless of whether the patients are symptomatic. The AACE also recommends insulin for patients with HbA1c levels more than 9% above normal if the patients are symptomatic.

### Introducing insulin

Patients’ fear, discomfort, and lack of adherence with insulin therapy, as well as certain societal factors, can impact achievement of treatment goals. Patients failing to initiate prescribed insulin therapy commonly have misconceptions regarding insulin risk. One study indicated that 35% of such patients believe that insulin causes blindness, renal failure, amputations, heart attacks, strokes, or early death. Many patients see the need for insulin as personal failure in self-care. Common characteristics among patients who fail to initiate

### Table 1. Change in glycosylated hemoglobin levels

<table>
<thead>
<tr>
<th>FPG (mg/dL)</th>
<th>Response</th>
<th>Change in units</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>Reduce dose by 3 units</td>
<td>–3</td>
</tr>
<tr>
<td>80-110</td>
<td>No Change</td>
<td>+0</td>
</tr>
<tr>
<td>&gt;110</td>
<td>Increase dose by 3 units</td>
<td>+3</td>
</tr>
</tbody>
</table>

Patient self-titration of basal insulin analog, with dose adjustment every 3 days on basis of fasting plasma glucose level.14,11
insulin therapy include a sense of personal failure, low self-efficacy, injection phobia, hypoglycemia concerns, inadequate health literacy, and limited insulin self-management training, as well as having health care providers who inadequately explain risks and benefits.17

Recent data show that patients who are non-adherent with clinic visits and insulin therapy are more likely to have higher HbA1c levels and face an increased risk for all-cause mortality compared to adherent compliant patients.18 These data demonstrate the importance of ensuring that patients with diabetes mellitus are knowledgeable and comfortable with insulin therapy.

To facilitate psychological receptiveness to injectable treatments among patients, physicians can encourage patients to self-monitor their blood glucose, they can educate patients about acceptable ranges for blood glucose readings, and they can discuss HbA1c results with patients. Providing patients with injectable pen delivery devices and establishing a structured program of support during insulin initiation may also help patients overcome their anxieties about treatment.19 Other factors to consider for facilitating insulin therapy include the following:

- Address the patient’s beliefs about insulin.
- Assess the patient’s insulin experiences.
- Determine the best insulin regimen for the patient.
- Determine the best delivery device for the patient.
- Educate the patient about dose adjustment.
- Adjust the insulin regimen as necessary.

**Basal insulin analogs**

Long-acting insulin analogs (eg, insulin glargine and insulin detemir) are now firmly established as key tools in the battle against diabetes mellitus, and ongoing clinical research is focused on treatment strategies to maximize the benefits of these agents. Basal insulin analogs provide relatively uniform insulin coverage throughout the day and night, primarily by controlling blood glucose levels through the suppression of hepatic glucose production between meals and during sleep.20 These agents are traditionally dosed once daily, at the same time each day. Recent data from the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial showed that insulin glargine had no positive or negative effect on cardiovascular outcomes and no association with cancer in patients with type 2 diabetes.21

Although basal insulin analogs are associated with a lower risk of hypoglycemia than human neutral protamine Hagedorn (NPH) insulin, hypoglycemia is a dose-limiting adverse effect of these agents.22 Patients using basal insulin therapy are more likely to adhere to treatment if they are prescribed a long-acting basal analog (eg, detemir or glargine vs NPH)23 and if they are able to administer insulin using a pre-filled pen (compared to the use of a vial and syringe).24

Continuation of oral medications along with basal insulin is a common clinical practice. The use of metformin mitigates insulin-associated weight gain and provides another mechanism of action by which to control hyperglycemia. Sulfonylureas may or may not be continued, depending on the patient and the physician’s clinical experience. Sulfonylureas are insulin secretagogues, and their use with insulin may increase the risk of hypoglycemia in some patients. Physicians are more likely to stop the use of sulfonylureas as the number of insulin doses increase; they should certainly consider discontinuing them regardless of the number of insulin doses if unacceptable hypoglycemia occurs, because the
sulfonylureas are most likely the culprits. Patients should be counseled about the signs and symptoms of hypoglycemia, including hypoglycemia prevention and treatment. Patients expressing concern about the possibility of insulin-related hypoglycemia should be reassured that the risk of this condition is low for patients with T2DM who are treated with basal insulin analogs, even among older adults. This risk is low despite the fact that patients with T2DM, because of an innate insulin resistance, tend to require higher doses of insulin than patients with type 1 diabetes mellitus. In the case of Sam, if hypoglycemia were to occur, discontinuation of the sulfonylurea would be advisable.

**Patient self-titration**
Basal insulin is most often initially used in patients with T2DM who fail to achieve optimal glycemic control with oral antidiabetic drugs. Clinical trials have shown that addition of a basal insulin analog to an oral regimen is capable of lowering the HbA1c level by approximately 1.6%, with of a once-daily basal insulin analog with a simple-to-use titration algorithm is a safe and effective intervention that may address some of the concerns of physicians related to the complexity of initiating insulin therapy.

Regarding glucose self-monitoring, physicians should consider urging measurements of fasting levels and “bracketing” 1 meal with preprandial and postprandial measurements daily on a repetitive basis. In addition, it should be kept in mind that Medicare allows 3 insulin measurements per day. Patients can get more if needed with additional documentation.

**Intensification of insulin therapy**
Titration of the patient’s existing insulin regimen is the first step in intensification efforts to maintain HbA1c goals. However, as T2DM takes its natural course of progression, treatment regimens need to be monitored and, when necessary, further intensified to maintain acceptable glycemic control. Physicians should consider intensifying therapy beyond titration of basal insulin when a patient using basal insulin has an HbA1c level above goal despite having achieved the FPG target. The addition of a sulfonylurea or an increase in sulfonylurea dose will not correct this glycemic problem and may actually increase the risk of hypoglycemia. Sulfonylureas first lower FPG, then lower PPG. Furthermore, simply increasing the dose of basal insulin in such a scenario is likely to expose the patient to the risk of between-meal hypoglycemia and persistent postprandial hyperglycemia.

Clinical experience suggests that the total daily insulin dose—on the basis of unit per kilogram of body weight—typically ranges from 0.5 to 2 units per kilogram per 24 hours for patients with T2DM. Approximately 50% of a patient’s total daily insulin dose is basal insulin, with the balance allocated across mealtime glucose spikes (ie, postprandial insulin). Thus, if the patient has not achieved HbA1c goals, attention to postprandial hyperglycemia is warranted. Adding prandial insulin to basal insulin regimens provides physiologic coverage of insulin requirements by means of switching to a premixed insulin analog or addition of a rapid-acting analog at mealtimes, as indicted in
Figure 2 and Table 2, provides considerations regarding which type of prandial coverage may be most suitable for a given patient. While basal-bolus insulin therapy required more injections, it tends to increase day-to-day life flexibility.

Given Sam’s erratic schedule, premixed insulin is not a desirable treatment option for him. Because he will likely need to titrate prandial insulin doses according to meal times and sizes, the addition of a prandial insulin at the largest meal is the most attractive option. Data from the Orals Plus Apidra and LANTUS (OPAL) trial showed that a single bolus of prandial insulin analog improved HbA1c levels when added to a basal insulin analog and oral antidiabetic agents (Figure 3).

**Challenges in adding medications to therapeutic regimens**

Recent data suggest that most patients with diabetes mellitus have negative perceptions of the initiation of additional medications, viewing it as evidence of personal failure and increased burden. Patients equate medication intensification with increased risk for diabetes-related complications rather than a step in reducing risk. They view de-escalation of medication as their primary goal. However, patients respond favorably to an individualized medication plan outlining future contingencies. According to the international Diabetes Attitudes, Wishes, and Needs (DAWN) study, more than half (57%) of all patients with T2DM are very worried about starting insulin therapy.

Many factors contribute to this worry. As previously noted, feelings of failure or depression (regarding following lifestyle changes and adherence to therapy), as well as the sense that using insulin means that their diabetes has worsened, may lead to resistance to insulin therapy. Many patients who are resistant to insulin therapy may also be reluctant to accept the responsibilities of everyday management of insulin therapy. Insulin should be offered to patients in a positive light—as a means to improve their health. Reminding them early in the disease that there may be times insulin is needed in a pinch, such as a critical illness or hospitalization, may help. This approach might facilitate their acceptance of insulin therapy. Physicians can help patients at the time of diagnosis by explaining that diabetes mellitus is a progressive disease, and that changes in therapy over the course of a lifetime in no way reflect badly on the patient.

**Table 2. Criteria for choosing between premixed vs basal-bolus insulin.**

<table>
<thead>
<tr>
<th>Premixed Insulin (1, 2, or 3 injections of same insulin)</th>
<th>Basal-Bolus Insulin (4 injections; 2 types of insulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preference for few injections</td>
<td>Variable meal pattern</td>
</tr>
<tr>
<td>Fixed daily routine</td>
<td>Variable daily routine</td>
</tr>
<tr>
<td>Unwilling to monitor blood glucose*</td>
<td>Postprandial control an issue</td>
</tr>
<tr>
<td>Limited cognitive function*</td>
<td>Able to comply with complicated regimen (eg, willing and good cognitive function)</td>
</tr>
<tr>
<td>Limited healthcare support system*</td>
<td>Support system available</td>
</tr>
<tr>
<td>*the last 3 apply when relaxed glucose targets are applied</td>
<td></td>
</tr>
</tbody>
</table>
Many patients have misconceptions about insulin therapy. Some of these misconceptions relate to the fact that insulin therapy was formerly delayed until the patient had advanced disease, often with complications. Thus, physicians may hear that the patient's grandmother started insulin therapy and shortly thereafter was on dialysis or had an amputation as a result of peripheral neuropathy—family experiences that cause the patient to associate the start of insulin therapy with a bad outcome. In Sam's case, he associated insulin therapy with his grandmother's diabetic complication of blindness.

It is important to ask patients what they think they know about insulin therapy. They should be informed about advances in insulin therapy—such as the availability of insulin analogs that reduce hypoglycemia risks (a valid concern) and that are convenient to dose (so as not to pose a lifestyle constraint), as well as the availability of insulin pen delivery devices (which should allay concerns about pain, embarrassment, and worries regarding correct dosing). All patients need to understand that in T2DM, the ability of the body to make insulin decreases over time. Helping patients understand the role of insulin in the management of T2DM and in the context of the disease process may go a long way to avoiding patient resistance to insulin use.

### Challenges in ethnic minorities

Type 2 diabetes mellitus is more common among African Americans and Mexican Americans than among non-Hispanic whites, which necessitates that primary care physicians consider culturally competent approaches to care. Mexican Americans and non-Hispanic blacks are less likely to achieve good glycemic control compared with non-Hispanic whites. Data from the National Health and Nutrition Examination Survey reveal that the disparity in diabetes-related mortality across education levels widened from the late 1980s to 2005—both overall and in the subgroups of men, women, blacks, whites, and Hispanics. Hispanics are generally much more concerned about adverse effects related to diabetes medications than are African Americans or non-Hispanic whites. Hispanics are also much more likely to be resistant to the idea of insulin therapy.

Ultimately, minority patients with diabetes mellitus are more likely than white patients with this condition to have poor long-term outcomes, leading to such complications as diabetic retinopathy, lower extremity amputations, and chronic kidney disease. Increasing clinicians' awareness of such racial and ethnic disparities and improving communication between clinicians and minority patients may enhance care among these patients. Language barriers may hinder adequate care by limiting or preventing communication (including the exchange of important cultural information) and by leading to misunderstanding of physicians' instructions, poor shared decision-making, and ethical compromises (eg, not obtaining full informed consent). In the Translating Research Into Action for Diabetes (TRIAD) study, 23% of Spanish-
speaking Hispanic patients reported language to be a barrier in communicating with health care professionals. Poor adherence to treatment, missed appointments, and patient dissatisfaction can all be attributed to miscommunication.

**Patient education and support**

The use of support groups for patients with diabetes mellitus that focus on management and education, creative ways to adopt healthy foods that complement ethnic diets, exercise opportunities, and other advice is an additional way to enhance self-management. Encouraging patients to use social networks of family members, peer support groups, community health workers, and one-on-one interactive education can improve patient resilience to stressors. Diabetes self-management education programs for Hispanics and Latinos, led by community health workers, have been implemented in a number of community settings. These programs may effectively improve behavioral skills, such as physical activity and healthy eating.

**Key learning points**

- Effectively educate patients with diabetes mellitus about the progression of and treatment for the disease.
- Achieving good glycemic control early prevents diabetic complications. The lowest possible HbA1c level, without unacceptable hypoglycemia and untoward complications, should be attained.
- Optimal glycemic control should be maintained to minimize the risk of diabetic complications. When choosing the treatment option for each patient, consider the duration of T2DM, stage of the disease, current level of control, lifestyle habits, and attitude toward disease management.
- Intensification of treatment requires glucose monitoring and medication adjustment every 2 to 3 months.
- Lifestyle intervention remains the foundation of care for all patients with diabetes mellitus, and healthy lifestyle choices should be addressed at every office visit.
- Most patients who have HbA1c levels greater than 7.5% will require combination therapy with complementary mechanisms of action.
- Insulin should be prescribed for all patients with HbA1c levels greater than 10% and for all symptomatic patients with HbA1c levels greater than 9%.

**References**


