Insulin Therapy for Challenging Patient Cases

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Initiating and advancing insulin therapy in patients with type 2 diabetes mellitus can be challenging. However, with the availability of insulin analogs with more physiologic profiles, and with the initiation of simple insulin regimens (eg, the use of basal insulin administered once daily), an opportunity is created to empower patients to self-titrate their insulin. Self-titration can reduce the burden on the physician as well as improve glycemic control in patients. More options for intensifying insulin now exist, including gradually adding prandial insulin (referred to as a basal “plus” strategy) or using premixed insulin analogs for patients with relatively consistent lifestyles and habits. More-concentrated forms of insulin, such as U-500 insulin, may be helpful for patients requiring very large doses of insulin. The key is to match the insulin regimen to the patient; engage in dialogue to understand the patient’s lifestyle, concerns, and skill sets; and develop, through a shared decision-making process, appropriate individualized treatment recommendations. The present review article focuses on the use of insulin replacement therapy in challenging patient cases.


Editor's Note: A correction to this article was published in the July 2013 issue of The Journal of the American Osteopathic Association (2013;113(7):507). The correction has been incorporated in this online version of the article, which was posted July 2013. An explanation of the change is available at http://www.jaoa.org/content/113/7/507.2.full.
Approximately 26 million people in the United States have diabetes, and the vast majority have type 2 diabetes mellitus (T2DM). Even with the establishment of treatment goals and the development of considerable advancements in diabetes treatment, inadequate metabolic control is pervasive. The proportion of patients with glycated hemoglobin ($\text{HbA}_1c$) levels that are at goal is still well below the diabetes indicators discussed in the Healthy People 2020 initiative. Available data show that many patients with T2DM still have poor glycemic control along with comorbid conditions that may complicate treatment decisions. These conditions include a high prevalence of hypertension, heart failure, stroke, and nephropathy, as well as other comorbidities associated with T2DM. When glycemic control is not optimized, diabetes imposes burdensome care requirements, increased health care costs, and a high risk of disabling complications. These situations are especially evident in socioeconomically disadvantaged and minority populations, who are already at higher risk for diabetes. Achieving reductions in $\text{HbA}_1c$ levels through a combination of clinical management and effective self-management has demonstrated a reduced risk of microvascular complications. More personalized approaches to therapy are needed.

Despite the well-documented benefits of both timely glycemic control and consensus guidelines that encourage the therapeutic use of insulin earlier in the course of T2DM, considerable clinical inertia exists with respect to initiating appropriate insulin therapy in patients with T2DM. The present article will explore some challenging cases for which the use of insulin is indicated, initiated, and adjusted, albeit not always with immediate patient acceptance.

General Principles

Since 2012, treatment algorithms for the management of patients with T2DM have followed the approach to patient-centered care established by the Committee on Quality of Health Care in America: “providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.” Diabetes management includes the setting of individualized glucose targets to achieve $\text{HbA}_1c$ levels as close to normal as possible in patients who are most likely to benefit from good glycemic control (ie, those without clinical evidence of macrovascular complications) while also minimizing the possible risks of hypoglycemia. It also includes relaxing targets in patients with limited life expectancy, in patients with existing diabetes complications or longer duration of disease, and in those for whom there is greater concern about the development of hypoglycemia.

Initiation of Insulin Therapy

When prescribing insulin therapy, the astute osteopathic physician implements the most appropriate form on the basis of the insulin type, dose, and delivery device used. For most patients whose $\text{HbA}_1c$ levels are not at goal, the simplest first step is to start insulin therapy with a single injection of a long-acting basal insulin analog. Basal insulin suppresses hepatic glucose production overnight and between meals. It constitutes approximately 50% of the daily insulin needs of an individual. Once-daily use of a basal insulin analog (insulin glargine or insulin detemir) offers the advantages of simple dosing and ease of titration (ie, patients can learn to manage their T2DM with limited training). This treatment is highly effective in improving glycemic control in patients who no longer respond to combination oral antidiabetic therapy. The goal of basal insulin analog therapy is to improve fasting blood glucose levels. Typical starting doses are 10 to 20 U of insulin glargine or insulin detemir given once daily (or, as an alternative, 0.2 U/kg). Neutral protamine Hagedorn (NPH) insulin can be a more economical option, but physicians should be aware that NPH insulin is more of an intermediate-acting insulin and that it therefore must be dosed 2 to 3 times per day to serve as a basal insulin. Physicians should also be aware that NPH insulin is associated with a greater risk of hypoglycemia, especially nocturnal hypoglycemia, than are basal insulin analogs.

Oral antidiabetic agents are usually continued when insulin is started, unless there are specific contraindications or substantial risks of hypoglycemia (in some cases, the dose of sulfonylureas may be decreased or discontinued). This continuance of therapy helps pa-
tients avoid the loss of further glycemic control during the transition to insulin. The insulin dose should be titrated on the basis of a fasting blood glucose target. The American Diabetes Association recommends a goal of less than 130 mg/dL. A patient should expect an approximately 0.5% decrease in the HbA\textsubscript{1c} level for each insulin dose increment of 0.1 U/kg per day. Basal insulins can be self-titrated up to either a target fasting blood glucose level or an approximate dose of 0.5 U/kg per day. At higher doses, the improvement in the decrease in the HbA\textsubscript{1c} level is less substantial, and the risk of hypoglycemia increases. If, after sufficient time, the HbA\textsubscript{1c} level still has not reached goal with the use of 0.5 U of basal insulin per kilogram per day, then attention should be focused on meal-time or prandial glucose excursions. If excursions are present, consider adding an agent to target postprandial hyperglycemia, which is the likely cause of persistent hyperglycemia. This can be confirmed by having the patient check his or her glucose level 2 hours after the meal. A number of options exist for the treatment of prandial hyperglycemia, including prandial insulin (eg, a fast-acting insulin or rapid-acting insulin analog, such as insulin lispro, insulin aspart, or insulin glulisine) or an incretin-based therapy (eg, a dipeptidyl peptidase-4 [DPP-4] inhibitor [such as sitagliptin, saxagliptin, or linagliptin] or a glucagon-like peptide-1 [GLP-1] receptor agonist [such as exenatide (administered twice per day), liraglutide (administered once per day), or exenatide (administered weekly)]). Exenatide extended release is not currently approved by the US Food and Drug Administration for use with insulin therapy.

Proactively Addressing Hypoglycemia

Hypoglycemia has always been the rate-limiting step in achieving perfect glycemic control for patients with T2DM. Hypoglycemia can be dangerous, and assessing patients for this condition is critically important. For patients, a fear of hypoglycemia can often have a considerable negative impact on diabetes management, metabolic control, and subsequent health outcomes. Not performing this assessment may result in patients taking such actions as engaging in “defensive” eating or omitting insulin doses to preclude hypoglycemia, thus thwarting the best efforts of the physician to help patients achieve glycemic control. This behavior becomes particularly dangerous if the physician is titrating insulin regimens.

Failure to address even mild hypoglycemia and glycemic control early in the course of T2DM may compromise the success of treatment in the long term. Fear of hypoglycemia certainly affects the willingness of the patient to accept insulin therapy, so it is vital to choose regimens carefully and to address this topic with patients. Some hypoglycemia may occur in association with insulin therapy, even when the most skilled physicians and knowledgeable patients are involved in its use. Thus, identifying hypoglycemia and providing prompt, appropriate treatment are paramount. The body may respond to extremely low nocturnal blood glucose levels by rebounding with high blood glucose levels in the morning (referred to as the Somogyi effect). This rebound could be incorrectly identified as fasting hyperglycemia. Both the patient and the physician should routinely review blood glucose patterns. Patients with type 1 diabetes mellitus, as well as those with T2DM of long duration, may be at risk of hypoglycemia. With increasing age, the potential reaction time between awareness and onset of symptoms is decreased, contributing to an increased risk for asymptomatic hypoglycemia and greater susceptibility to cognitive impairment. Recurrent, unrecognized hypoglycemia can occur even in patients with T2DM who have well-controlled glycemia. Asymptomatic hypoglycemia and nocturnal hypoglycemia can interfere with the ability of patients to recognize subsequent hypoglycemia, and they can also limit patients’ ability to take appropriate action, thereby exacerbating the situation. This outcome, known as hypoglycemic unawareness, is a marker of a high risk of severe hypoglycemia.

Furthermore, high glucose variability (blood glucose excursions occurring throughout the day) may be a predictor of diabetic complications, independent of HbA\textsubscript{1c} levels, in patients with T2DM. As a result, because patients fear hypoglycemia, they may be reluctant to follow or adjust their insulin regimens when needed. This lack of action may result in chronic hyperglycemia, oxidative stress, and the risk of long-term...
complications. Better daily control of blood glucose excursions, especially in the postprandial period, may reduce glucose variability in patients with T2DM and may also reduce the risk of complications.

Intensifying Therapy
For patients who require intensification of insulin therapy, strategies may include sequentially adding prandial insulin doses and then switching to pre-mixed insulin (which provides basal and prandial insulin in a single injection, albeit in a fixed-dose ratio) or full basal-bolus dosing (which involves multiple daily injections of insulin). Patients who have severe insulin resistance (eg, those who require more than 200 U of insulin) may benefit from receiving concentrated insulin formulations (eg, 500 U/mL, as opposed to 100 U/mL for most insulins). Providing very large doses of less concentrated insulin may result in difficulties with reliable insulin absorption because of simple volume problems.

Case Study: Edith
Edith, a 74-year-old African American woman (weight, 100 kg), presents with substantial osteoarthritis (OA) of the hip that requires total hip replacement. Her surgeon has reported that he will not operate until Edith’s diabetes is better controlled. Edith has T2DM of 10 years’ duration. Although her T2DM initially had been controlled through lifestyle changes and metformin therapy, she is currently taking 1000 mg of metformin twice daily and 10 mg of glipizide twice daily. Her current HbA1c level is 10.8%. Edith checks her fasting blood glucose level every morning. She has a history of OA and hypertension and has undergone percutaneous transluminal coronary angioplasty. She reports wanting to be more active.

Assessment
Edith has uncontrolled T2DM and is likely to have comorbidities. Her renal function should be checked. (Older patients and those with elevated HbA1c levels are at greater risk for evidence of renal impairment, which may influence the approach to antihyperglycemic therapy.) Edith’s serum creatinine level is 1.2 mg/dL; however, her glomerular filtration rate is 65 mL/min/1.73 m².

Considerations and Precautions Related to Antihyperglycemic Agents
Metformin should be avoided if Edith’s serum creatinine level is 1.4 mg/dL or higher (a serum creatinine level of ≥1.5 mg/dL is the cutoff for men). Because of the risk of hypoglycemia, sulfonylureas should be used cautiously in patients with renal impairment. If a sulfonylurea is used, glipizide is preferred because of its route of excretion. If insulin is chosen—which is likely because Edith’s blood glucose level needs to be lowered expeditiously before her operation—more modest dosing and the use of insulin analogs are warranted to minimize the risks of nocturnal hypoglycemia. Whereas prescribing information for the basal insulin, insulin glargine, indicates that it may be given either in the morning or evening, insulin detemir indications are for administration in the evening only. In clinical practice, both insulin analogs can be given at any time of day. If nocturnal hypoglycemia is the major concern, a basal insulin analog can be administered in the morning; this may be an off-label use, but it will allow the physician and the patient to become comfortable with the dosing and titration of the insulin. In setting a treatment goal for Edith, it is noted that her current HbA1c level is 10.8%. Insulin is very effective at lowering blood glucose levels, with its dose limited only by hypoglycemia. However, that is a strong caveat to consider, especially in an older patient. Increased age and impaired renal function are considered risk factors for hypoglycemia.

Considerations for Diabetes of Long Duration
The diabetes guidelines from the US Department of Veterans Affairs and the US Department of Defense (VA/DoD) were updated in 2010. As with other guidelines, the VA/DoD guidelines do not distinguish treatment goals by age group. However, they do provide some guidance that may be applicable to this case study: “for the patient with longer duration diabetes (more than 10 years) or with comorbid conditions and who requires a combination medication regimen including insulin should have an A1C target of <8%.” If following these guidelines, physicians may set one goal for the preoperative period and...
any signs or symptoms of hypoglycemia. Her blood glucose data logs show improvements not only in her fasting glucose levels but also in her postprandial glucose levels (Table 2).

In this case study, Edith undergoes the operation and rehabilitation and then resumes walking. When she returns to the physician’s office, her HbA1c level is 6.4%. Edith now checks her glucose levels only in the morning and whenever she feels like her blood glucose levels are low (Table 3), which sometimes occurs when she is “out and about.” She carries food with her, “just in case.” If Edith experiences “low blood sugar,” she sometimes decides to skip her insulin dose the next day. Her current antihyperglycemic medication regimen consists of 1000 mg of metformin twice daily and 10 mg of glipizide twice daily; she also takes 62 U of basal insulin analog once daily. Evidence of documented hypoglycemia exists, as do signs of increased glucose variability in the aforementioned patterns. The basal insulin analogs have stable profiles, and patients who are receiving stable doses should have stable glucose profiles. Edith's lifestyle is now limited by hypoglycemia; she is experiencing symptoms, eating defensively.

### Table 1. Physician-Directed or Patient-Driven Treat-to-Target Titration Algorithms for Basal Insulin Analogs

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean of Self-Monitored FPG Values,* mg/dL</th>
<th>Change in Insulin Dose, U/d General</th>
<th>Physician Directed</th>
<th>Patient Managed</th>
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</thead>
<tbody>
<tr>
<td>Riddle et al⁵⁹</td>
<td>≥180</td>
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<td>NA</td>
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<td>100-120</td>
<td>+2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Davies et al⁴⁰</td>
<td>≥180</td>
<td>NA</td>
<td>+6 to +8</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>140-179</td>
<td>NA</td>
<td>+4</td>
<td>+2</td>
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<td>+2</td>
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<td></td>
<td>100-119</td>
<td>NA</td>
<td>0 to +2</td>
<td>0 to +2</td>
</tr>
<tr>
<td>Meneghini et al⁴¹</td>
<td>&gt;110</td>
<td>+3</td>
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<td>NA</td>
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<td>NA</td>
</tr>
<tr>
<td></td>
<td>&lt;80</td>
<td>−3</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Means were calculated from data obtained on 2 successive days for Riddle et al⁵⁹ and from data obtained on 3 successive days for Davies et al⁴⁰ and Meneghini et al.⁴¹

Abbreviations: FPG, fasting plasma glucose; NA, not applicable.
skipping insulin doses, and possibly experiencing hypoglycemia without being aware of it. Table 4 summarizes the signs and symptoms of hypoglycemia, whereas Table 5 shows the physiologic responses to hypoglycemia. At Edith's age, and with her lifestyle-limiting symptoms, the most important step is to address her hypoglycemia.

It is very important to educate patients about the signs and symptoms of hypoglycemia. The body has multiple defenses with which to prevent hypoglycemia, but age and a history of hypoglycemia can affect the body's hypoglycemic threshold for symptoms and when it can respond. The first line of defense is suppression of insulin production; the second is increased glucagon secretion. These 2 steps prevent most occurrences of hypoglycemia in people without diabetes or in individuals with T2DM of limited duration. If the blood glucose levels continue to drop after suppression of insulin and secretion of glucagon, then release of epinephrine, cortisol, and growth hormone will follow. At even lower blood glucose levels, defensive eating is observed as a response.

Patients with type 1 diabetes mellitus are missing the 2 aforementioned lines of defense, which is why they are more prone to hypoglycemia than are patients with T2DM. However, by the time patients with T2DM require insulin, they are physiologically similar to patients with type 1 diabetes mellitus. These patients with T2DM of longer duration are at greater risk for hypoglycemia than are younger patients with T2DM (Figure 1).

Medication Adjustment
Concerns about hypoglycemia are discussed with Edith, and it is agreed that the glipizide dose will be reduced to 10 mg given once daily, and the basal insulin analog dose is reduced to 52 U. She is asked to send in her blood glucose readings 2 weeks after making this medication adjustment. At that time, her morning blood glucose level is more stable, and the hypoglycemia has stopped. Edith says that she notices that she needs to eat snacks a lot less often.

Six months later, Edith's fasting blood glucose levels are at goal (Table 6), but her HbA1c level is elevated, suggesting that her hypoglycemia persists. The most important step is to address her hypoglycemia.

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**Figure 1.**

Thresholds for symptomatic hypoglycemia vary with age. With increasing age, the potential reaction time between awareness and onset of symptoms is decreased, contributing to an increased risk for asymptomatic hypoglycemia and a greater susceptibility to cognitive impairment. Age designations are presented as mean [standard deviation] years. Data are for nondiabetic patients with no family history of diabetes. Reprinted with permission from the American Diabetes Association, from Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care*. 2005;28(12):2948-2961 and from Matyka K et al. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. *Diabetes Care*. 1997;20(2):135-141; permission conveyed through Copyright Clearance Center, Inc.
short-acting and long-acting insulins. People who have erratic daily schedules and mealtimes or people who skip meals would not be good candidates for premixed insulin regimens. Regarding premixed insulin, it is also important to differentiate between the human and the analog formulations available. The pharmacokinetics are remarkably different because the short-acting insulin in the human formulation is regular insulin, which has a very different pattern of action than the rapid-acting analog insulins (insulin aspart and insulin lispro) in the analog formulations.

Given Edith’s history, a single dose of prandial insulin is added before her largest meal; she is asked to check preprandial and postprandial glucose levels at dinner (her biggest meal) and to check her morning glucose levels less often. We reduce her basal analog insulin dose and discuss her sending in monthly readings to help with titration of her therapy. With her age and need or switch to a premixed insulin analog by dividing the total basal dose in half and administering it twice daily before breakfast and dinner.32,44 Ideally, the patient should have a regular, stable, daily treatment schedule to minimize the risk of hypoglycemia resulting from these fixed-dose products. Concern surrounds the low levels of blood glucose noted at 3 to 5 hours after injection, when there is overlap in the action of the

### Table 2.
**Glucose Diaries: Edith’s Preoperative Blood Glucose Levels With Addition of Basal Analog Insulin**

<table>
<thead>
<tr>
<th>Week</th>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
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<tr>
<td>Morning</td>
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<td>242</td>
<td>210</td>
<td>160</td>
<td>188</td>
<td>160</td>
<td>164</td>
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<tr>
<td>Evening</td>
<td>240</td>
<td>286</td>
<td>200</td>
<td>268</td>
<td>200</td>
<td>168</td>
<td>240</td>
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<td></td>
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</tr>
<tr>
<td>Morning</td>
<td>148</td>
<td>140</td>
<td>140</td>
<td>128</td>
<td>120</td>
<td>122</td>
<td>114</td>
</tr>
</tbody>
</table>
| Evening | ... | 154 | ... | 158 | ... | 148 | ...

or switch to a premixed insulin analog by dividing the total basal dose in half and administering it twice daily before breakfast and dinner.32,44 Ideally, the patient should have a regular, stable, daily treatment schedule to minimize the risk of hypoglycemia resulting from these fixed-dose products. Concern surrounds the low levels of blood glucose noted at 3 to 5 hours after injection, when there is overlap in the action of the

### Prandial Correction Insulin
Several options are available for introducing prandial correction insulin, including adding a single injection of prandial insulin to the largest meal or the meal with the highest postmeal glucose level (a basal “plus” strategy), providing basal-bolus insulin (in multiple daily injections), or using premixed insulin (which provides basal and prandial insulin in a single injection). The basal “plus” strategy can be used to transition to the use of basal-bolus insulin (Figure 2). When the patient’s HbA1c level is not at goal after 1 injection of basal insulin analog, options include adding a rapid-acting insulin analog before meals. If this is done, then the physician should subtract 10% of the basal dose and add that amount to the largest meal,43 or switch to a premixed insulin analog by dividing the total basal dose in half and administering it twice daily before breakfast and dinner.32,44 Ideally, the patient should have a regular, stable, daily treatment schedule to minimize the risk of hypoglycemia resulting from these fixed-dose products. Concern surrounds the low levels of blood glucose noted at 3 to 5 hours after injection, when there is overlap in the action of the

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**Figure 2.**
Strategy for switching from basal to basal-bolus insulin.
for insulin at mealtime, it appears that Edith is no longer responding to the sulfonylurea, so it will be removed as part of her titration. One month later, she is taking 46 U of basal insulin and 6 U of a rapid-acting insulin analog at dinner. We then stop the glipizide and increase her insulin dose at mealtime to 12 U. After another month, we reduce her basal insulin because she has further increased her activity level. With increased activity, and with less snacking caused by defensive eating, Edith has lost 10 lbs and is feeling good about her progress (Table 7). Edith is taking metformin (1000 mg twice daily), a basal insulin analog (40 U) in the morning, and a rapid-acting insulin analog (12 U) before dinner. Edith is so pleased with her results that she refers her son, William.

Case Study: William
William is a 52-year-old man who works as an accountant. He has had diabetes mellitus for 15 years, and his current HbA1c level is 9.6%. William takes 80 U of basal insulin analog twice daily. He also takes 10 U of rapid-acting insulin at meals, when he remembers to do so; he takes it, on average, twice daily. His blood glucose levels are not low. William also has hypertension, dyslipidemia, and obstructive sleep apnea (OSA).

The Challenge of the “Diabetes Belt”
Localized predominantly in the southern states and Appalachia, the “Diabetes Belt” is an area of the United States where the incidence of diabe-
tes is 11.7%, compared with the 8.7% incidence in the rest of the country (Figure 3).45 Nearly one-third of the increased risk of diabetes among individuals in the Diabetes Belt is associated with a sedentary lifestyle and obesity.46 There also are more African Americans with diabetes in the Diabetes Belt than in other areas of the United States. William shares some of the characteristics of individuals from the Diabetes Belt (Figure 4).46 He also has OSA, which is another common comorbidity of T2DM. Primary care providers tend to underdiagnose OSA in patients with T2DM,47 so William’s OSA is something to consider.

**Poor Glycemic Control in the Face of High Insulin Doses**

Physicians should always remember to confirm treatment adherence in patients who experience poor glycemic control while ostensibly receiving very high doses of insulin therapy. Inspection of injection sites and review of injection technique are also important, because injection-related problems have been known to affect glycemic control. Many patients will develop changes in the subcutaneous tissue, including lipohypertrophy or lipoatrophy. This scarring or dimpling of the skin will also affect insulin absorption. Check to make sure that insulin is not expired or denatured. In William’s case, he had many vials of “used” insulin in his house; many vials were not dated when he started to use them, and some had clearly expired. In addition, it should be noted that large doses of insulin may produce a depot effect (albeit less so with analog insulin).
U-500 insulin is also very helpful for people who need more than 300 U of insulin per day and still have uncontrolled hyperglycemia. U-500 is a human regular insulin, but its time-action profile is not the same as that of the usual U-100 formulation. It has the same peak as U-100 regular insulin, but its duration is more like that of NPH insulin (approximately 12 h). Given these characteristics, U-500 works as both basal and prandial (bolus) insulin, so patients who use it not only take less insulin by volume, but they also typically need only one type of insulin. The use of U-500 insulin has also been associated with increased patient satisfaction and cost savings.

U-500 insulin is 5 times as potent as U-100 insulin. When converting U-100 insulin dosing to U-500 dosing, if the total daily insulin dose is less than 200 U, first divide by 5 and then split to twice-daily dosing (with 60% of the total daily dose given before the morning meal and 40% given before the evening meal). If the total daily dose is more than 200 U, first divide by 5 and then use thrice-daily dosing (at break fast, lunch, and bedtime). In William's case, he takes a total of 180 U per day; \( \frac{180 \text{ U}}{5} = 36 \text{ U} \), William can take 22 U before breakfast and 14 U before dinner. This allows William to obtain insulin coverage with only 2 injections. This dosing provides a less physiologic profile than what William was previously taking, but he shows increased adherence with this treatment and improves his glycemic control.

### Table 6. Glucose Diaries: Edith's Blood Glucose Levels 6 Months After the Operation

<table>
<thead>
<tr>
<th>Blood Glucose Levels, mg/dL</th>
<th>Time</th>
<th>Mon</th>
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<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
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<td>...</td>
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</tr>
</tbody>
</table>

* Edith's glycated hemoglobin level is 8.5%. She checks her glucose levels in the morning and whenever she feels that her glucose levels are low.

### Table 7. Glucose Diaries: Edith's Blood Glucose Levels 12 Months After the Operation

<table>
<thead>
<tr>
<th>Blood Glucose Levels, mg/dL</th>
<th>Time</th>
<th>Mon</th>
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<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
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</thead>
<tbody>
<tr>
<td>Morning</td>
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<td>...</td>
<td>125</td>
<td>...</td>
<td>120</td>
<td>...</td>
<td>105</td>
</tr>
</tbody>
</table>
| Postprandial                |        | ... | 135 | ... | 140 | ... | 160 | ...

* Edith's glycated hemoglobin level is 6.7%. She checks her glucose levels intermittently.

and may be associated with unpredictable absorption.\(^{48}\) It is more likely that William was not actually absorbing the full dose of insulin that he was injecting.

### U-500 Insulin

Some patients with T2DM are profoundly insulin resistant and require very large doses of insulin for glycemic control. Large volumes of subcutaneous conventional U-100 insulin can cause discomfort at the injection site, resulting in poor patient adherence to insulin therapy. Furthermore, the depot effect may change insulin absorption as mentioned above. A therapeutic option that clinicians should be aware of is the use of U-500 insulin (Humulin R U-500; Eli Lilly and Company, Indianapolis, Indiana), which substantially reduces the volume of insulin to be injected.\(^{49}\) Obese patients with uncontrolled T2DM who are severely insulin resistant can achieve satisfactory glycemic control with the use of U-500 regular insulin administered either by subcutaneous injection or via insulin pump.\(^{33,50,51}\)

Candidates for U-500 insulin include patients who have immune-mediated insulin resistance, lipoatrophic diabetes, antibodies against the insulin receptor, genetic abnormalities of the insulin receptor, or obesity.\(^{52}\) U-500 insulin is commonly used for people who need more than 300 U of insulin per day and still have uncontrolled hyperglycemia. U-500 is a human regular insulin, but its time-action profile is not the same as that of the usual U-100 formulation. It has the same peak as U-100 regular insulin, but its duration is more like that of NPH insulin (approximately 12 h). Given these characteristics, U-500 works as both basal and prandial (bolus) insulin, so patients who use it not only take less insulin by volume, but they also typically need only one type of insulin. The use of U-500 insulin has also been associated with increased patient satisfaction and cost savings.\(^{34}\)

U-500 insulin is 5 times as potent as U-100 insulin. When converting U-100 insulin dosing to U-500 dosing, if the total daily insulin dose is less than 200 U, first divide by 5 and then split to twice-daily dosing (with 60% of the total daily dose given before the morning meal and 40% given before the evening meal). If the total daily dose is more than 200 U, first divide by 5 and then use thrice-daily dosing (at breakfast, lunch, and bedtime). In William's case, he takes a total of 180 U per day; because 180 U/5 = 36 U, William can take 22 U before breakfast and 14 U before dinner. This allows William to obtain insulin coverage with only 2 injections. This dosing provides a less physiologic profile than what William was previously taking, but he shows increased adherence with this treatment and improves his glycemic control.
Conclusion

Insulin remains our most effective agent for lowering blood glucose levels. Insulin formulations continue to be developed and refined, and they will likely continue to be essential in the management of T2DM. Physicians should feel comfortable initiating insulin therapy at any stage of T2DM, and they should be able to teach patients to self-titrate their insulin. Insulin therapy should be intensified in a patient-centric fashion, using the method that best fits each patient’s profile, including adding prandial insulin, using full basal-bolus therapy, switching to premixed insulin therapy, or using more-concentrated insulin formulations. It is beneficial for patients to titrate insulin themselves, using parameters that let them know what dose or events signal the need to stop titration. Glucose variability and hypoglycemia are unexpected and warrant a call to the physician. By increasing patient levels of comfort with regard to insulin therapy, improved rates of glycemic control can be achieved.

References


The Future of Insulin Therapy for Patients With Type 2 Diabetes Mellitus
Joseph M. Tibaldi, MD

Insulin therapy has been the mainstay of therapy for patients with type 2 diabetes mellitus for the past 90 years. This trend is likely to continue as new formulations are developed to more closely mimic physiologic insulin secretion and to provide patients who have diabetes with more convenient options for integrating this therapy into their lifestyle. The present article reviews how the role of insulin continues to evolve, from its earlier use in the treatment paradigm (even at first diagnosis) to its role in combination therapy with incretin-based therapies, as well as new formulations that provide more-convenient forms of insulin replacement therapy.

J Am Osteopath Assoc. 2013;113(4 suppl 2):S29-S39
The number of patients with type 2 diabetes mellitus (T2DM) far exceeds the number of endocrinologists and diabetes specialists available to treat them. The majority of patients are treated in primary care environments, and by virtue of the common comorbidities that “travel” with diabetes, including hypertension, dyslipidemia, and obesity or overweight, comprehensive and holistic approaches to care are required. Osteopathic physicians are likely to encounter more and more such patients in their practices. As a result of improvements in health care and increases in longevity, patients are more likely to require insulin therapy at some point during the progression of T2DM. With advances in insulin therapy still occurring, it is well worth keeping up to date on trends in the use of this powerful glucose-lowering agent.

Patients with T2DM are insulin resistant, have relatively low insulin production, or have both characteristics. Most patients with T2DM eventually require insulin if other medications fail to control their blood glucose levels adequately. Insulin replacement therapy lets patients know that a key component of their natural glucose-regulating system is being restored. When insulin replacement therapy was introduced more than 90 years ago, it was a lifesaving option for patients with type 1 diabetes mellitus (T1DM), even though the formulations used were relatively crude. During past decades, major advances in our ability to synthesize more reproducible and physiologic formulations have enabled the production of much more sophisticated and patient-friendly agents. The present review article discusses initiation of insulin replacement therapy at the time of diagnosis, basal insulin therapy used in combination with incretin therapy, and second-generation basal insulin analog therapy, using a case study to demonstrate clinical application. Other means of enhancing delivery of insulin to patients are also discussed.

Pathophysiologic Profile of T2DM Drives Treatment Choices

Insulin is instrumental in managing T2DM, which is a complex, multihormonal, and progressive chronic disease. Our approach to the treatment of patients with T2DM requires an understanding of the pathophysiologic profile of this condition to determine when and how to use the many pharmacologic agents available.

Type 2 diabetes mellitus results from the abnormal secretion or abnormal actions of key hormones that regulate glucose production by the liver and glucose uptake in the peripheral muscle and adipose tissue. In patients with established T2DM, insulin secretion is reduced because of progressive loss of pancreatic β-cell function. Plasma glucose levels increase as insulin deficiency and insulin resistance reduce normal insulin activity, leading to diminished stimulation of peripheral glucose uptake and decreased inhibition of hepatic glucose production.

Glucagon normally helps maintain fasting plasma glucose levels by stimulating hepatic glucose production. In patients with T2DM, the normal postprandial suppression of glucagon secretion is inadequate, leading to increased hepatic glucose output that worsens hyperglycemia. In turn, chronic hyperglycemia leads to glucose toxicity that paradoxically results in reduced synthesis and secretion of insulin. Native glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the gut that normally slows gastric emptying, acts on the pancreas to stimulate glucose-dependent insulin secretion, and suppresses the release of glucagon. Incretin deficits or incretin resistance may result in the abnormal regulation of insulin and glucagon secretion that characterizes T2DM. Like insulin, GLP-1 and glucagon are important targets of pharmacologic treatment strategies for improving glycemic control.

Use of Insulin Therapy Early in the T2DM Treatment Paradigm

Insulin remains integral to the treatment of patients with diabetes. For patients with T1DM, insulin therapy is essential and lifesaving. For patients with T2DM, use of insulin therapy was formerly relegated to use during later stages of the disease. This approach is being reexamined as more recent treatment paradigms encourage earlier use of insulin treatment algorithms for patients with T2DM. On the basis of guidelines from the American Association of Clinical Endocrinologists, insulin therapy clearly is recommended for patients with severe hyperglycemia and for pa-
tients receiving oral antidiabetic drugs who have glycated hemoglobin (HbA1c) levels greater than 9%.12

Of particular interest are data assessing the use of insulin as a first-line treatment option for T2DM, often in patients who initially have very high levels of glucose toxicity. This treatment option was reviewed by Rolla13 in 2009, and additional data have since been published. Several studies14-16 have shown prolonged remission of T2DM in patients receiving intensive insulin therapy for 2 weeks. A 2- to 3-week course of intensive insulin therapy can lay the foundation for prolonged good glycemic control in patients with newly diagnosed T2DM who have elevated fasting glucose levels. Figure 1 shows an example of the effects of short-term intensive insulin therapy on glucose and insulin levels.14

In a more recent study, the use of low-dose insulin therapy (given as premixed insulin in one study) for patients with newly diagnosed T2DM led to evidence of β-cell recovery, as documented by plasma insulin and C-peptide levels.17 It appears that reversing glucose toxicity may result in a rapid improvement in β-cell function, which then allows the β cell to start to function and to secrete adequate amounts of insulin for clinically significant periods of up to 1 year.14-16 This series of events is also known as a “second-wind” phenomenon for the β cell.13 After symptom relief occurs and glucose levels are normalized in such patients, oral agents often can be added to therapy, and it may be possible to withdraw insulin.

Figure 1. Glucose and insulin levels before insulin therapy, immediately after insulin therapy, and 1 year after insulin therapy, demonstrating the effects of short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes mellitus.14 Reprinted with permission from the American Diabetes Association, from Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes mellitus. Diabetes Care. 2004;27(5):1028-1032; permission conveyed through Copyright Clearance Center, Inc.
Other recent data show that β-cell function can be preserved for at least 3.5 years with the use of early and intensive T2DM therapy involving administration of either insulin plus metformin or triple oral therapy after an initial 3-month period of insulin-based treatment. These data support the premise that insulin should not be relegated to use as a last-line therapy but, rather, could be used earlier in the disease paradigm, when some β-cell function remains intact. Insulin therapy can be discontinued in patients who have early disease, and it can be restarted when necessary or continued in conjunction with other oral agents or GLP-1 receptor agonists.

### Case Study

**Harry**

Harry is a 52-year-old man who, for the past 6 months, has been struggling with a new job that has required his attention during most of his waking hours. His past medical history includes hypertension, for which he takes a diuretic, and mixed hyperlipidemia managed with a modest dose of a statin.

Harry has been fastidious in taking his medications, but his job keeps him at his desk most of the time. His only exercise is walking to the local fast food restaurant where he buys most of his meals. The owner of the restaurant noted that Harry was returning more frequently and buying more juice and soda. The owner’s wife had diabetes, so the owner gently questioned Harry about his thirst levels and weight loss, thinking that he might have diabetes. After talking with the owner, Harry realized that he had unquenchable thirst. He promptly made an appointment to see his primary care physician, even though he had been negligent in doing so for the past year.

The findings from Harry’s visit to his physician were notable. He had a weight loss of 15 lbs, a nonfasting glucose level of 430 mg/dL, an HbA1c level of 12%, and trace levels of ketone bodies in his urine sample. Insulin replacement therapy was recommended as initial treatment.

In Harry’s case, insulin therapy was clearly indicated. He had T2DM, clinically significant hyperglycemia, and signs of catabolism (weight loss), and no oral agent or other noninsulin agent would begin to bring him close to his goal HbA1c level. Pathophysiologic findings revealed that his liver was secreting excess glucose that was unable to enter the muscle. His problematic glucose levels occurred in part because Harry has diminished insulin levels. However, it also occurred because Harry has a GLP-1 deficit, and because, with that deficit, he was producing too much glucagon.

It is gratifying to treat a patient like Harry, who arrives at the office feeling poorly but who, after approximately 3 to 6 months, is in much better health and can have blood glucose levels that are close to normal. Chronic hyperglycemia leads to reduced insulin secretion (Figure 2). By reversing glucotoxicity, it is possible for the body to resume insulin secretory capacity.

### Harry, 2-Year Follow-Up

Harry’s diabetes treatment regimen now includes basal insulin as well as metformin. During the 2 years since Harry was first seen in the physician’s office, he has been self-titrating his basal insulin and has generally been able to keep his HbA1c level at less than 7%. However, despite engaging in exercise on a relatively consistent basis, he has gained 11 lbs. For the past 6 months, however, his HbA1c level has been 8.3%, in spite of fasting blood glucose levels between 90 and 115 mg/dL. Harry’s goal is to once again attain an HbA1c level of less than 7%.

Many patients who receive basal insulin therapy will ultimately require treatment intensification. Notably, the HbA1c level reflects not only fasting blood glucose levels but also postprandial glucose levels. Adding a sulfonylurea to insulin-based therapy increases the risk of hypoglycemia without providing much benefit. Sulfonylureas also lower fasting glucose levels much more than postprandial glucose levels, so they may not be the best treatment option for Harry. At this point, the clinical decision traditionally is to switch to a premixed insulin or move toward a basal-bolus regimen (which is often done by sequentially adding prandial insulin before meals as needed and as tolerated). This clinical decision is certainly a well-validated and effective treatment strategy, but there are drawbacks for some patients—namely, an increased risk of hypoglycemia, weight gain, and number of complications for patients in terms of the number
of injections needed and the complexity of titrating both basal and prandial insulin doses.23

**Basal Insulin Therapy in Combination With Incretin-Based Therapy**

Another approach used to augment insulin therapy is to add incretin-based agents to the treatment regimens of patients who are receiving basal insulin therapy but who are no longer achieving treatment goals. Although these approaches are similar, they have important differences (Figure 3).9 Glucagon-like peptide-1 receptor agonists provide supraphysiologic levels of the incretin hormone and have greater efficacy in lowering glucose levels.24-27

The benefit of using these approaches is that incretin-based therapies work in a glucose-dependent manner (ie, only in the presence of hyperglycemia). They also are weight neutral (dipeptidyl peptidase-4 [DPP-4] inhibitors) or are associated with weight loss (GLP-1 receptor agonists).

Currently, DPP-4 inhibitors, as well as both liraglutide and short-acting exenatide, are approved for use with long-acting basal insulin analogs in patients with T2DM who are not achieving their goals for glycemic control. Incretin-based therapies primarily target postprandial hyperglycemia (although longer-acting GLP-1 agonists also affect fasting plasma glucose levels) and lower postprandial glucose levels, with a low associated risk of hypoglycemia and without weight gain (an advantage over prandial insulin analogs).28-33

However, basal insulin doses may need to be adjusted downward or sulfonylureas may need to be discontinued.34

Table 1 provides a summary of some of the available published literature on DPP-4 inhibitors used in combination with insulin therapy.28,29,35

The use of GLP-1 agonists in combination with insulin therapy for postprandial glucose control also may result in some weight loss.33 Some clinicians prefer to start with a GLP-1 agonist or an incretin-based therapy early in the treatment paradigm, before initiating insulin.36,37
Case Study Revisited

Harry Follow-Up

Harry was presented with options to help him return to his goal HbA\textsubscript{1c} level of 7%. A DPP-4 inhibitor would be a simple treatment option but would not allow him to attain this goal. A successful treatment option that could achieve this goal is the addition of prandial insulin injections at mealtimes.

Harry was also concerned about losing weight, so it was decided to use GLP-1 receptor agonists. Because Harry was traveling a great deal and eating at irregular times (usually at a restaurant), he wanted a simple treatment plan that involved the least number of injections and a medication that did not require strict dosing in relation to meals. Therefore, once-daily liraglutide was selected. Liraglutide is administered once daily, without regard to mealtime, but it

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**Table 1.** Outcomes of Select Studies of Dipeptidyl Peptidase-4 Inhibitors in Combination With Insulin Over 24 Weeks Duration

<table>
<thead>
<tr>
<th>Source</th>
<th>Agent</th>
<th>Comparison</th>
<th>Patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong et al, 2012\textsuperscript{28}</td>
<td>Sitagliptin</td>
<td>Add-on to insulin vs an insulin dose increase</td>
<td>Patients with T2DM (n=140); baseline HbA\textsubscript{1c} level, 9.2%</td>
<td>Compared with a 25% increase in the insulin dose, adding sitagliptin to an insulin-based regimen was more effective at lowering HbA\textsubscript{1c} levels and was associated with less hypoglycemia and weight gain</td>
</tr>
<tr>
<td>Barnett et al, 2012\textsuperscript{23}</td>
<td>Saxagliptin</td>
<td>Insulin alone or insulin plus metformin, addition of saxagliptin vs placebo</td>
<td>Patients with T2DM (n=455); baseline HbA\textsubscript{1c} level, 7.5% to 11%</td>
<td>Addition of saxagliptin improved glycemic control and was generally well tolerated</td>
</tr>
<tr>
<td>Vilsbøll et al, 2010\textsuperscript{29}</td>
<td>Sitagliptin</td>
<td>Add-on to basal or premixed insulin vs placebo</td>
<td>Patients with T2DM (n=451); baseline HbA\textsubscript{1c} level, 7.5% to 11%</td>
<td>Addition of sitagliptin improved glycemic control and was generally well tolerated</td>
</tr>
</tbody>
</table>

**Abbreviations:** HbA\textsubscript{1c}, glycated hemoglobin; T2DM, type 2 diabetes mellitus.

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**Table 2.** Comparison of Onset, Peak, and Duration of Longer-Acting Basal Insulins

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral protamine Hagedorn</td>
<td>1-2 h</td>
<td>4-8 h</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Glargine</td>
<td>30-60 min</td>
<td>Relatively peakless</td>
<td>16-24 h</td>
</tr>
<tr>
<td>Detemir</td>
<td>30-60 min</td>
<td>Relatively peakless</td>
<td>16-24 h</td>
</tr>
<tr>
<td>Degludec</td>
<td>30-90 min</td>
<td>Peakless</td>
<td>&gt;24 h</td>
</tr>
</tbody>
</table>

**Source:** Reprinted from Nasrallah SN, Reynolds LR. Insulin degludec, the new generation basal insulin or just another basal insulin? Clin Med Insights Endocrinol Diabetes. 2012;5:31-37.\textsuperscript{38} Copyright 2012, with permission from Libertas Academica Ltd.
should be administered at approximately the same time each day, if possible. Short-acting exenatide is administered twice daily before meals. It should be noted that the once-weekly formulation of exenatide is not currently approved by the US Food and Drug Administration (FDA) for use with insulin.

The physician discussed the possibility of nausea occurring in association with initiation of GLP-1 receptor agonist therapy. The nausea tends to be mild to moderate and of a transient nature. Harry was told that if severe nausea or abdominal pain were to occur, he would need to call the physician’s office right away, because the presence of these symptoms might be a sign of a more serious condition, such as pancreatitis.

Harry’s basal insulin dose was reduced by 20%, from 40 U to 33 U, at night. When basal insulin is used with GLP-1 receptor agonists, the need for lower doses of insulin has been observed. There also is the possibility that patients may transiently eat less if nausea is problematic, which may increase the possibility of insulin-related hypoglycemia developing. Furthermore, by means of mechanisms independent of adverse gastrointestinal effects, patients treated with GLP-1 receptor agonists experience greater satiety than placebo-treated patients, and their food intake may decrease.

Harry already knew how to use an insulin pen delivery device, so he was told to start with a dose of 0.6 mg of insulin given subcutaneously daily. One week later, Harry increased the insulin dose to 1.2 mg given subcutaneously daily.

A follow-up appointment was scheduled for 6 weeks after Harry started using the insulin pen. At that visit, mild nausea had occurred; however, it abated 3 weeks later. Harry had a weight loss of 5 lbs, and he noted that his fasting blood glucose level was still between 80 and 120 mg/dL.

The next follow-up visit occurred after Harry had been receiving the new medication for 12 weeks. At that time, he had lost an additional 4 lbs, and his HbA1c level was 6.8%.

What Else Is New?

**Ultra-Long-Acting Basal Insulin in Development**

Current research efforts are focusing on improving the pharmacokinetics and pharmacodynamics of long-acting insulin analogs to make them even less variable and longer acting (ie, make them truly once-daily insulin analogs). These
Advances have been made in the clinical development of both insulin degludec (administered alone or in combination with insulin aspart) and pegylated insulin lispro. Insulin degludec has been shown to have a longer duration of action, which can be beneficial for patients who require insulin at a consistent time each day.

Table 3: Published Trials of Ultra-Long-Acting Insulins

<table>
<thead>
<tr>
<th>Source</th>
<th>Insulin Agent</th>
<th>Patient Characteristics</th>
<th>Insulin Comparator</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenstock et al, 2013&lt;sup&gt;36&lt;/sup&gt;</td>
<td>LY2605541 (pegylated insulin lispro)</td>
<td>T1DM; basal-bolus therapy</td>
<td>Glargine</td>
<td>8-wk randomized, phase 2, open-label, 2×2 crossover study</td>
<td>Greater improvements in glycemic control, increased total hypoglycemia, reduced nocturnal hypoglycemia, reduced weight, and lowered insulin doses at mealtime</td>
</tr>
<tr>
<td>Bergenstal et al, 2012&lt;sup&gt;37&lt;/sup&gt;</td>
<td>LY2605541 (pegylated insulin lispro)</td>
<td>T2DM (HbA&lt;sub&gt;1c&lt;/sub&gt; level &lt;10.5%); metformin and/or sulfonylurea with glargine or NPH insulin once daily</td>
<td>Glargine</td>
<td>12-wk, randomized, open-label, phase 2 study</td>
<td>Comparable glucose control; total hypoglycemia rates, reduced intraday variability, and lower nocturnal hypoglycemia, as well as weight loss, relative to glargine</td>
</tr>
<tr>
<td>Birkeland et al, 2011&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Degludec</td>
<td>T1DM; mean HbA&lt;sub&gt;1c&lt;/sub&gt; level 8.4%</td>
<td>Glargine</td>
<td>16-wk, randomized, phase 2 controlled trial</td>
<td>Comparable glucose control at similar doses, with reduced rates of hypoglycemia</td>
</tr>
<tr>
<td>Heise et al, 2011&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Degludec/ aspart</td>
<td>T2DM; background metformin therapy</td>
<td>Glargine</td>
<td>16-wk, open-label trial</td>
<td>Comparable glucose control at similar doses, similar low rates of hypoglycemia, and better glucose control after dinner</td>
</tr>
<tr>
<td>Zinman et al, 2012&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Degludec</td>
<td>T2DM; background therapy for OAD; baseline HbA&lt;sub&gt;1c&lt;/sub&gt; level 7% to 10%</td>
<td>Glargine</td>
<td>1-year treat-to-target, open-label, randomized trial</td>
<td>Comparable glucose control, much lower rates of nocturnal hypoglycemia</td>
</tr>
<tr>
<td>Heller et al, 2012&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Degludec</td>
<td>T1DM; basal-bolus insulin therapy; HbA&lt;sub&gt;1c&lt;/sub&gt; level &lt;10%</td>
<td>Glargine</td>
<td>1-year treat-to-target, open-label, randomized trial</td>
<td>Comparable glucose control and much lower rates of nocturnal hypoglycemia</td>
</tr>
<tr>
<td>Garber et al, 2012&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Degludec</td>
<td>T2DM; basal-bolus insulin; HbA&lt;sub&gt;1c&lt;/sub&gt; level, 7% to 10%</td>
<td>Glargine</td>
<td>1-year treat-to-target, open-label, randomized trial</td>
<td>Comparable glucose control and much lower rates of overall and nocturnal hypoglycemia</td>
</tr>
<tr>
<td>Niskanen et al, 2012&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Degludec/ aspart (twice daily) and an alternative formulation</td>
<td>T2DM; HbA&lt;sub&gt;1c&lt;/sub&gt; level 7% to 11%</td>
<td>Biphasic insulin aspart twice daily</td>
<td>16-wk, open-label, randomized, treat-to-target trial</td>
<td>Comparable glucose control and lower rates of hypoglycemia</td>
</tr>
</tbody>
</table>

**Abbreviations:** HbA<sub>1c</sub>, glycated hemoglobin; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drugs; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

longer-acting insulin analogs will be more forgiving of the busy schedules of patients, because they have little to no impact on glucose levels if there is some variation in the time of administration. Optimal glycemic benefits are achieved with the injection of current basal insulin analogs at a consistent time each day, on the basis of their duration of action. Table 2 provides a comparison of the pharmacodynamics of longer-acting insulin analogs. The goal of ongoing research is to come close to achieving glycemic control while benefiting from a reduced risk of hypoglycemia and more convenience for the patient.
gludec has been submitted to the FDA for review. This ultra-long-acting basal insulin has a flat and stable glucose-lowering effect,\textsuperscript{41} and it is associated with a much lower risk of nocturnal hypoglycemia than insulin glargine, as has been demonstrated in studies of patients with T1DM and T2DM.\textsuperscript{42-47} The pharmacodynamic variability of insulin degludec is much lower than that of insulin glargine.\textsuperscript{41,48} Insulin degludec has received an approvable status from an FDA regulatory panel and has been approved for use in Europe.

Because insulin degludec has a stable and prolonged time-action profile, coupled with low within-subject variability, it allows for more-flexible once-daily dosing. Insulin degludec has a flat and stable glucose-lowering effect that is not affected by dose.\textsuperscript{48} This concept was tested in patients with T2DM participating in a 26-week randomized trial\textsuperscript{49} in which insulin degludec (administered in variable dosing intervals in a flexible regimen) was compared with insulin glargine (administered at the same time each day). Both insulins were added to an existing regimen of oral glucose-lowering therapy, as in the case study described here, and study patients were titrated to achieve fasting plasma glucose levels of less than 90 mg/dL. The once-daily regimen of insulin degludec involved a compulsory, rotating morning-and-evening schedule of dosing that created 8- to 40-hour dosing intervals. From a baseline HbA\textsubscript{1c} level of 8.4\%, HbA\textsubscript{1c} values were reduced by 1.28\% and 1.26\% with the use of insulin degludec and insulin glargine, respectively. Low rates of hypoglycemia were noted with both regimens. This trial\textsuperscript{49} showed that insulin degludec can be administered at varying times without resulting in either a loss of glycemic control or the development of hypoglycemia to accommodate changes in a patient’s daily schedule.

Another new agent, pegylated insulin lispro, is currently moving into phase 3 of clinical development. This agent appears to be associated with less variability, less nocturnal hypoglycemia, perhaps slightly more overall hypoglycemia (which may be related to some dosing and titration issues), and some interesting effects on weight. To my knowledge, few data on this compound have been published in the peer-reviewed literature to date.

A summary of available data from clinical trials is shown in Table 3.\textsuperscript{54-56} Overall, these exciting developments may be used by physicians to improve glycemic control and to increase patient acceptance of and adherence to insulin therapy.

**Inhaled Insulin**

Inhaled insulin has been under development for many years, but a product that actually reached market (Exubera, an insulin human [recombinant DNA origin] inhalation powder; Pfizer, New York, New York) was eventually withdrawn because of poor market uptake,\textsuperscript{51} perhaps because of the complex requirements for its administration.\textsuperscript{52} Other inhaled insulin agents that have been investigated have been found to produce nocturnal hypoglycemia.\textsuperscript{53}

Technosphere insulin (MannKind Corporation, Valencia, California), another inhaled insulin, was compared with subcutaneous regular human insulin in a randomized, open-label study of their efficacy and safety in covering prandial insulin needs.\textsuperscript{54,55} Technosphere insulin substantially improved postprandial glucose levels and had a more favorable pharmacodynamic profile than subcutaneous regular human insulin. The Technosphere insulin system is currently undergoing phase 3 trials.

All of these efforts illustrate the difficulty of working with complex proteins, such as hormones, and highlight the successes that have been achieved with current and emerging formulations as they continue through the approval process.

**Oral Insulin**

The physiologic barriers of the gastrointestinal tract pose a major challenge for the optimal delivery of any hormone, including insulin. Oral insulin would provide a convenient method of administration, potentially leading to improved glycemic control for patients with poor adherence to subcutaneous insulin regimens.\textsuperscript{2}

**Conclusion**

Development of insulin replacement therapy is ongoing. Physicians need to understand the central role of insulin in the pathophysiologic profile of diabetes, how it can be used early or late in the disease process, and how it complements other agents. As more insulin
products become available, an understanding of the relative characteristics, benefits, and potential of these agents in helping us to improve glycemic control in patients currently coping with unsatisfactory glycemic control cannot be overstated.

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