INTRODUCTION
Currently, we are in the midst of an obesity epidemic that has led to an unprecedented rise in the incidence of type 2 diabetes mellitus. Early and intensive glycemic control is necessary to prevent or minimize the development of microvascular and macrovascular complications in patients with type 2 diabetes; however, the majority of patients with type 2 diabetes do not achieve adequate glycemic control. Current treatment recommendations call for rapid addition of medications and transition to new regimens when glycemic goals are not achieved. Insulin therapy is the most effective therapy for lowering glycemia. However, barriers to its use exist. This manual will discuss the metabolic management of type 2 diabetes with a focus on insulin therapy.

CASE STUDY

INITIAL PRESENTATION
A 47-year-old woman presents to the office of an internist as a new patient after having recently moved to the area.

HISTORY
The patient was diagnosed with type 2 diabetes 5 years previously, at which time her glycated hemoglobin (A1c) was elevated at 6.8%. The patient was started on lifestyle modification and shortly thereafter began metformin, which she titrated to a dose of 1 g twice daily. At the time of her diagnosis, she was also started on a statin and an angiotensin-converting enzyme inhibitor. The patient did well over the next 2 years, with her A1c values ranging from 6.2% to 6.5%; however, at a follow-up examination approximately 30 months after the diagnosis, her A1c was noted to be elevated at 7.2%. At that time, her physician started her on a sulfonylurea (glimepiride), and after this intervention the patient again did well, with improved glycemic control over the next 2 years (A1c values, 6.5%–6.9%).

At this visit, the patient reports that she checks her blood glucose levels once daily and occasionally after meals. Recently she has noticed progressively elevated readings, in particular, her AM readings, which are greater than 200 mg/dL on average. To her knowledge, she has never experienced an episode of hypoglycemia. Her lipid levels and blood pressure have been well controlled. Her dilated retinal examinations, urine microalbumin-to-creatinine ratio studies, and baseline serum creatinine levels have been unremarkable.

PHYSICAL EXAMINATION
The patient is 163 cm (5 ft 4 in) in height and weighs 79.8 kg (176 lb), with a body mass index of 30 kg/m². Physical examination reveals a blood pressure of 129/80 mm Hg and a heart rate of 72 bpm. Other physical examination findings are unremarkable. Laboratory work obtained the day of the visit is remarkable for an A1c of 8.0%.

- What are the current recommendations for the management of hyperglycemia in type 2 diabetes?

In 2006, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes released a consensus algorithm for the management of hyperglycemia in type 2 diabetes. An update was published in 2008 addressing safety issues regarding the thiazolidinediones, and a revised consensus statement was released in 2009. The guidelines recommend that an A1c of 7% or greater should serve as a call to action to initiate or change therapy, with the goal of achieving an A1c as close to the nondiabetic range as possible or, at minimum, decreasing the A1c to less than 7%. Step 1 of the algorithm calls for initiation of lifestyle interventions and metformin at the time of diagnosis (Figure). Sustained weight loss and increased levels of activity have a beneficial effect on control of glycemia and improve cardiovascular risk factors such as blood pressure and lipids. However, noting the difficulty of
sustained weight loss coupled with the progressive nature of diabetes, the guideline authors also recommend concurrent metformin therapy at the time of diagnosis. Because of its beneficial effects on glycemic control and absence of weight gain coupled with a relatively low level of side effects and low cost, metformin is the initial agent of choice and should be titrated to the maximally tolerated dose.

Patients who do not reach glycemic goals within 2 to 3 months should be started on step 2. The preferred route of therapy for step 2 is the addition of basal insulin or a sulfonylurea (Tier 1 of algorithm). In selected clinical settings, Tier 2 of the algorithm may be considered.

- **How should this patient's current therapy be changed?**

  If lifestyle changes, metformin, and sulfonylurea or basal insulin do not result in achievement of target glycemia, the next step is to start or intensify insulin therapy (Figure).

**RATIONALE FOR INITIATING INSULIN**

Insulin is the oldest, most clinically utilized agent practitioners have in their armamentarium. Although initially developed for treatment of type 1 diabetes, insulin has been an effective agent in the setting of type 2 diabetes and insulin resistance for nearly 70 years. Because it has no set maximum dosage, insulin dosing can be safely and effectively titrated to meet the needs of the individual patient without predetermined therapeutic ceilings. Furthermore, the advent of insulin analogs and unique insulin delivery devices have allowed insulin therapy to more closely mimic physiologic insulin release.

The advantage of insulin versus adding a third oral
agent has been validated in clinical trials. In 2003, Schwartz et al\textsuperscript{8} studied 188 subjects with type 2 diabetes and inadequate response to 2 oral medications with A1c less than 8.0%. Patients were randomly assigned to treatment with either a third oral medication or an insulin 70/30 mix twice daily plus metformin. Results of the 24-week trial showed insulin 70/30 mix plus metformin was as effective as triple oral therapy in lowering A1c and fasting plasma glucose values. Additionally, triple oral regimen was not as cost-effective and had a high percentage of patients who were unable to complete the regimen due to lack of efficacy or side effects.

Although insulin therapy has long been seen as an agent of last resort, emerging data from a number of recent trials indicate early intensified therapy confers a number of metabolic advantages. The Epidemiology of Diabetes Interventions and Complications Study (EDIC)\textsuperscript{9} is an observational study that has followed the cohort from the Diabetes Control and Complications Trial (DCCT). In the EDIC study, the degree of glycemic control no longer differed significantly between the 2 original DCCT treatment groups at 7 years, although those patient who were treated intensively in the original DCCT trial had a 42\% reduction in any first cardiovascular event when compared with the conventionally treated group, and the risk of first occurrence of nonfatal myocardial infarction, stroke, or death from cardiovascular disease was reduced by 57\%. Similarly, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study\textsuperscript{10} demonstrated that patients with diabetes who received insulin infusion within 24 hours of myocardial infarction followed by subcutaneous insulin treatment for at least 3 months had a significantly lower mortality rate (19\%) at 1 year as compared with patients who received standard treatment (26\%). Similar findings of hyperglycemia and adverse outcomes in acute myocardial infarction have recently been published by Kosiborod et al.\textsuperscript{11}

- **What types of insulin preparations are available?**

  Currently available insulins include basal preparations used to suppress hepatic glucose production overnight and between meals (ie, intermediate-acting and long-acting insulins) and bolus preparations used to control blood glucose surge following meals (ie, rapid-acting and short-acting insulins); premixed, fixed-ratio formulations of intermediate-acting and rapid- or short-acting insulins also are available.

  With the advent of analog insulin therapy, which includes long-acting, rapid-acting, and premixed insulin, many of the problems and limitations of conventional therapy have been overcome. Insulin analogs were developed using recombinant DNA technology, which made minor alterations in the structure of native human insulin. With these minor modifications in structure, analog therapy offers more physiologic pharmacokinetic profiles, which not only provide a means by which intensive insulin therapy can be administered but also a more flexible schedule of replacement.\textsuperscript{12,13}

**RAPID-ACTING INSULIN ANALOGS**

Currently, 3 rapid-acting insulin analogs are available. All 3 have been shown to be superior to regular human insulin in reducing postprandial hyperglycemia secondary to their pharmacokinetic profile.\textsuperscript{14–16} These rapid-acting analogs work in a “quick on, quick off” fashion, as they reach higher peak insulin concentrations in half the time of equivalent doses of regular human insulin with a shorter duration of action than regular human insulin, closely mimicking normal physiologic insulin secretion.\textsuperscript{17} The predictability offered by these agents has also allowed for safer administration, as rapid-acting analogs have shown a reduced incidence of severe hypoglycemia and nocturnal hypoglycemia in patients with type 2 diabetes as compared with regular human insulin.\textsuperscript{15–17} Rapid-acting insulin analogs can be administered within 15 minutes of starting a meal or shortly after a meal has concluded, offering patients greater flexibility in regards to eating habits and has led to higher levels of patient treatment satisfaction in comparison with regular human insulin.\textsuperscript{16}

**LONG-ACTING INSULIN ANALOGS**

In addition to the rapid-acting agents, 2 long-acting insulin analogs are now available. Similar to the rapid-acting analogs, these agents offer considerable improvement in regards to glycemic control, safety, and patient satisfaction when compared with previous conventional therapy. Before the approval of the long-acting insulin analogs, intermediate-acting preparations such as isophane insulin (NPH) were frequently used as basal insulin. Both long-acting insulin analogs provide constant insulin levels, generally devoid of peaking. Coupled with longer duration of action as compared with NPH, both these long-acting analogs provide a more physiologic basal insulin replacement.\textsuperscript{18–20} Furthermore, these agents have considerably less within-subject variability in insulin absorption than NPH, and both agents can be administered once daily.\textsuperscript{19,20} In addition to the beneficial aspects of more closely mimicking endogenous release, these agents have lead to considerable improvement in delivery systems, including insulin pens that have allowed for improved patient compliance and accuracy of dosing while being easier to use.\textsuperscript{21,22}
Both long-acting insulin analogs for type 2 diabetes have been studied in treat-to-target trials in which patients enrolled had poor control on oral agents and received either of the basal insulin analogs or NPH. In these studies, insulin doses were actively titrated using a prespecified algorithm and plasma glucose monitoring to achieve target fasting plasma glucose levels. These treat-to-target studies have shown that the long-acting insulin analogs effectively control glycemia with less hypoglycemia compared with NPH.

**Should oral agents be continued when starting basal insulin?**

Several randomized controlled trials comparing insulin monotherapy with insulin plus metformin suggest a synergistic effect of combined therapy. Wulffele et al randomized 390 patients whose diabetes was controlled on insulin (mean baseline A1c < 8%) to metformin or placebo in addition to insulin. At 16 weeks, mean A1c was 6.9% in the combined therapy group versus 7.6% in the insulin-only group. Also, the insulin dose requirement was reduced by about 8 U/day, and there was a net weight loss of 0.4 kg compared with a mean weight gain of 1.2 kg in the insulin-only group. Similarly, Giugliano et al compared ongoing insulin monotherapy with metformin plus insulin in a 6-month placebo-controlled trial involving 50 patients. Compared with insulin monotherapy, combined therapy was associated with a 1.84% improvement in A1c level (from 11.7%–9.8%) and a 25% reduction in the daily insulin dose. In a small crossover study comparing insulin and metformin with insulin and placebo, Ponssen et al demonstrated a reduced insulin requirement (by approximately 8 U/day) and reduced A1c (–0.74%) favoring metformin plus insulin after 5 months of therapy.

While the thiazolidinediones have also been shown to be beneficial in conjunction with insulin in regards to A1c reduction, daily insulin dose reduction, and favorable changes in lipid profiles, they must be used with caution. In fact, coadministration of rosiglitazone with insulin is not recommended, and the ADA has recommended against using rosiglitazone in the treatment of type 2 diabetes. Fluid retention may occur with this class of drugs, which may exacerbate or lead to congestive heart failure. In addition, rosiglitazone may possibly increase the risk of myocardial infarction.

Practitioners who elect to use TZDs should start with a low dose and monitor closely for signs of edema, rapid weight gain, and other indicators of potential cardiovascular risk.

**CASE CONTINUED**

After a discussion with the patient, it is decided she will begin basal insulin therapy with a long-acting insulin analog and continue on her current doses of her metformin and sulfonylurea.

**What are important considerations when introducing patients to insulin therapy?**

One of the most important issues in introducing insulin is patient acceptance. Often, patients will have misconceptions about insulin therapy that need to be addressed to ensure optimal results. Education is often the best means by which to address concerns and is best done in a multidisciplinary fashion, including nursing, dieticians, and certified educators. Education should focus on the fact that type 2 diabetes is progressive in nature and that the need insulin for therapy should not be viewed as personal failure. The benefits of intensive glycemic control and the associated reduction of diabetes-related complications should also be emphasized. Fear of hypoglycemia is also a commonly encountered issue when initiating insulin. Patients should be educated about the signs and symptoms of hypoglycemia and given instructions for prevention and treatment of hypoglycemic episodes.

Self-monitoring of blood glucose (SMBG) is another critical aspect of therapy. The goal of SMBG should be to obtain detailed information about blood glucose levels during specific times of the day to ensure safety of the current regimen as well as for aiding in the adjustment of agents in response to blood glucose values. Measurement of fasting blood glucose allows assessment of the adequacy of basal insulin therapy, whereas tests before lunch, dinner, and at bedtime allow assessment of the adequacy of bolus therapy administered with breakfast, lunch, and dinner, respectively.

In initiating basal insulin, the rule of thumb is to start low and titrate steadily. Although the vast majority of patients with type 2 diabetes have significant insulin resistance and the eventual dose required to achieve glycemic targets is substantial, a safe starting dose in patients with type 2 diabetes is 0.15 U/kg body weight/day. Titration to an established target fasting blood glucose can be achieved with easy to use protocols that allow achievement of euglycemia while decreasing the risk of hypoglycemia.

**CASE CONTINUED**

The patient undergoes comprehensive diabetes education and successfully begins insulin therapy. Over the next several weeks, she titrates her
WEIGHT GAIN

Weight gain is an important side effect for many patients with type 2 diabetes undergoing intensification of therapy with insulin. Weight gain can cause distress and can compromise the intentions of a regimen aimed at improved control, particularly in a group of individuals who are already overweight and who are also being asked to concentrate on weight loss. In the United Kingdom Prospective Diabetes Study (UKPDS), obese patients who were treated with insulin over the 10-year period gained an average of 4 kg more than patients assigned to diet only therapy and 1.8 kg more than patients assigned to sulfonylurea treatment. Other studies of insulin therapy in type 2 diabetes have documented an average weight increase of 3% to 9% of pretreatment baseline weight. Furthermore, body composition studies have suggested that approximately two thirds of weight gained is adipose tissue, and the remaining third is lean body mass.

An important strategy for avoiding weight gain is to stress the importance of adopting and maintaining a healthy lifestyle that incorporates physical activity. While interventions promoting dietary changes and increasing exercise should be initiated at the time of diagnosis, they should be continued throughout the duration of treatment, particularly for patients who are overweight or obese. In addition to lifestyle interventions, therapeutic agents can also be used to help minimize associated weight gain. Concurrent use of metformin therapy with insulin is commonly recommended as a means of limiting weight gain in patients with type 2 diabetes. In addition, long-acting insulin analogs are known to have weight benefits.

HYPOGLYCEMIA

Hypoglycemia is defined clinically as an abnormally low blood glucose concentration in the presence of neurologic symptoms, the latter being rapidly reversed following glucose administration. Hypoglycemia is the most common side effect of insulin therapy, although it also may occur with the use of certain insulin secretagogues. Because insulin promotes cellular uptake of glucose and inhibits hepatic gluconeogenesis, therapy with exogenous insulin or long-acting insulin secretagogues predisposes a patient to hypoglycemia, and the lower the glycemic target, the more likely the occurrence of hypoglycemia. In the UKPDS, the incidence of hypoglycemia was 1.8% in patients treated with insulin and 1.4% in patients treated with sulfonylureas. Precipitating causes of hypoglycemia include missed meals, strenuous unanticipated exercise, alcohol consumption in the absence of food, and insulin overdosing errors. Mild hypoglycemia is characterized primarily by adrenergic symptoms (eg, sudden diaphoresis, nervousness, tremulousness) accompanied by urgent hunger. The appearance of such symptoms warns the patient that the blood glucose level is dropping, prompting appropriate action on the part of the patient. By contrast, severe hypoglycemia has been defined as the inability to self-treat symptoms, requiring assistance from another person or from emergency medical personnel. Symptoms of severe hypoglycemia impair the patient’s ability to take corrective action and include cognitive dysfunction such as confusion, amnesia, bizarre behavior, seizures, or coma. With the initiation of insulin, patients should be advised on how to manage dosing errors as well as educated in regards to the need to eat and exercise according to schedule, to test blood glucose levels whenever they may feel hypoglycemic, and to take corrective action to minimize severe hypoglycemic episodes.

CASE CONTINUED

Over the next 2 years, the patient experiences gradually increasing glycemia. At an interim visit roughly 3 years after beginning insulin therapy, her A1c is 8.3%, her fasting blood glucose values average 150 mg/dL, and her random blood glucose values average 180 mg/dL. Her weight has increased by 10 lb, but her physical examination, lipid profile, renal function, and ophthalmologic examination remain normal. The patient continues to be on maximal doses of her sulfonylurea and metformin.

• What are treatment options for this patient?
This case illustrates a scenario that commonly occurs in type 2 diabetes. When glycemia is no longer controlled with oral agents and basal insulin, intensification with prandial insulin is required. With a rising A1c and daytime random blood glucose values in the setting of maximum-dose sulfonylurea, it can be inferred that the patient is functionally unable to secrete endogenous insulin to meet mealtime demands for insulin. Basal insulin can no longer be titrated, as the patient will be at high risk for nocturnal hypoglycemia, and it would not address the postprandial hyperglycemia, which is the primary defect in this setting.

Potential options for advancement of insulin therapy to include prandial insulin include premixed therapy or basal-bolus therapy.

**PRE-MIXED INSULIN**

Pre-mixed insulin used in practice is generally given as twice-daily injections used to provide both basal and prandial insulin coverage. Several options are available commercially and include the mixture of 70% NPH insulin/30% regular insulin. Due to the peak effect of regular insulin, this mixture is most effective in attenuating postprandial hyperglycemia when given 30 minutes prior to the meal. With the advent of analog insulin, several newer combinations of pre-mixed insulin are now available and can be given with meals. Premixed insulin analogs have a rapid-acting component that is less likely to overlap with the protaminated insulin component and thus should lower postprandial glucose excursions with less hypoglycemia 4 to 6 hours after injection.

Dosing of premixed insulin analogs in type 2 diabetes can be initiated once or twice daily beginning with 6 to 12 U per dose. Titration protocols have been established through a number of clinical trials and have recommend adjusting the dose of insulin periodically according to blood glucose readings until glycemic targets are met. Through these titration schedules, appropriate insulin replacement in most patients was achieved by 12 to 16 weeks of therapy.

While the newer analog-based agents have improved pre-mixed therapy, they are somewhat limited in overall flexibility as the regimen does not closely mimic endogenous insulin secretion. As these mixtures contain a mixture of rapid- and longer-acting insulin, the end result is a single broad peak of insulin action between 3 and 6 hours after each injection. Because of its limitations, this type of replacement may be best served for those who prefer a simple, convenient insulin replacement schedule over a more intensive regimen with more frequent blood glucose monitoring with multiple daily injections.

**BASAL-BOLUS INSULIN**

The basal-bolus insulin regimen more closely mimics endogenous insulin release by incorporating continuous basal insulin release throughout the day and night, with brief increases in insulin levels at the time of meal ingestion through the administration of bolus doses. As blood glucose has 2 sources, dietary carbohydrates absorbed in the gut and hepatic gluconeogenesis, an ideal insulin replacement regimen provides adequate control of both sources. In persons without diabetes, prandial insulin is released into the portal circulation in response to increased blood glucose levels following a meal. This occurs in 2 phases: phase 1 insulin is released within seconds of ingestion of food, peaks in 1 to 2 minutes, and has a duration of about 10 minutes. This allows for suppressing hepatic glucose output, limiting postprandial rise in glucose, and stimulating phase 2 insulin release. Release of phase 2 insulin occurs at within 15 minutes of phase 1 and lasts for 1 to 2 hours. It is primarily responsible for lowering the postprandial rise in blood glucose. Basal endogenous insulin release occurs at a relatively continuous rate throughout the day, at a rate of approximately 0.5 to 1.0 U/hr. Basal insulin acts to maintain glycemic control in response to the continuous hepatic glucose production. In the setting of normal beta cell functioning, glycemic control is maintained via both prandial and basal insulin secretion. This general pattern is characterized by continuous basal secretion with intermittent bursts corresponding with meals, comprising prandial release.

Multiple daily injection therapy (MDI) most closely mimics this natural pattern, as long-acting agents provide the basal replacement controlling hepatic gluconeogenesis while the rapid-acting bolus analogs provide replacement needed to cover the postprandial period. Converting to MDI from a regimen consisting of basal insulin plus oral agents can be done sequentially, adding prandial insulin coverage at 1 or more meals per day, depending on the preferences of the patient and practitioner. Options include adding a prandial insulin dose before the largest meal of the day or using post-prandial blood glucose readings to determine which meal leads to the greatest glycemic excursion. The first dose of prandial insulin should be titrated based on either the 2-hour postprandial target (< 180 mg/dL) or the next preprandial glucose reading (target < 130 mg/dL). Once the first prandial dose of insulin has been appropriately adjusted, additional prandial doses can be added if A1c targets have not been achieved. This approach provides flexibility, as it can be tailored to the individual’s lifestyle, and it allows for a
smoother transition to a full MDI. During this transition phase, practitioners often face a therapeutic dilemma in regards to continuation of insulin secretagogues. As they are not considered synergistic when administered with insulin and may complicate titration, it is recommended secretagogues be discontinued or tapered.

Because most patients will eventually require prandial insulin coverage with every meal, it may be more conducive to therapy to provide prandial insulin with each meal at the time of intensification, with concurrent insulin secretagogue discontinuation.

For the case patient, the best course of action may be to discontinue the sulfonylurea and initiate prandial insulin at all 3 meals. Thus, the regimen would consist of 1 injection of basal insulin with a bolus injection of a rapid-acting analog 3 times daily with meals. Because the bolus component typically represents 40% to 50% of the total daily dose in such a regimen, one would expect that the case patient would eventually need a dose of 20 U of an insulin bolus preparation at each of 3 meals to provide adequate control. A starting dose of 10 U per meal would be safe starting and further titrations can be made based on measured blood glucose values obtained 2 hours after the meals with titration of in increments of 10% to 20% of the total daily dose every 3 to 7 days.

To help with the transition, nurse case management by telephone has been shown to be effective in helping patients adjust insulin doses incrementally toward target glycemic goals. And as titration continues, it is important to remember that there is no ceiling dose of exogenous insulin; the dose must be individually titrated to requirement to obtain the established goals of therapy.

**CASE CONCLUSION**

The patient agrees to discontinue her sulfonylurea and to start a basal-bolus insulin regimen consisting of the long-acting insulin analog and a rapid-acting insulin analog with each meal. The patient continues to take metformin. On follow-up evaluation 1 month later, the patient’s fasting blood glucose values average 110 mg/dL and her prandial glucose values average 160 mg/dL. Her mealtime insulin dose is increased. A follow-up appointment 2 months later finds the patient with a fasting blood glucose average of 100 mg/dL and prandial average of 135 mg/dL, with an improved A1c of 6.8%.

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**REFERENCES**


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