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ONLINE EXCLUSIVE

Insulin therapy for type 2 diabetes: Making it work

Initiating and advancing insulin therapy in patients with type 2 diabetes can be challenging. Here's how to overcome the barriers that may arise.

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PRACTICE RECOMMENDATIONS

- *Inform patients with type 2 diabetes about the possible need for insulin therapy if diet, healthy lifestyle, and medications other than insulin do not achieve glycemic control.* (A)
- *Add basal insulin to oral medications as soon as needed to help patients reach fasting glycemic goals. If further adjustments are needed, add prandial insulin.* (B)
- *Choose basal and prandial insulin analogs to approximate normal physiologic insulin secretion.* (C)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Many patients with type 2 diabetes will eventually require insulin to reach glycemic targets that have been shown to protect against micro- and macrovascular complications of the disease. But in the primary care setting, initiating and advancing insulin therapy for these patients can be challenging. This article discusses the barriers to initiating insulin therapy that family physicians often encounter and suggests strategies for addressing them. The goal should be to approximate normal physiologic insulin secretion as closely as possible. We will outline how that goal can best be achieved using combinations of long-acting and rapid-acting insulin analogs in a variety of basal-prandial regimens.

The evidence behind good glycemic control

Several landmark trials, including the United Kingdom Prospective Diabetes Study (UKPDS), the Diabetes Control and Complications Trial (DCCT), the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), and the recent ADVANCE study, demonstrate the importance of good glycemic control in reducing the risk of microvascular complications of diabetes.[1-4] These studies all show that lower glycosylated hemoglobin levels (hemoglobin A1C) are associated with a reduction in risk for the development or progression of microvascular complications of the disease.[1-4]

Setting glycemic targets

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have established guidelines that provide physicians and patients with glycemic targets. The ADA recommends that hemoglobin A1C be maintained at <7.0% or as near normoglycemia (<6.0%) as possible without significant risk of hypoglycemia. Preprandial glucose targets are 70 to 130 mg/dL, and the

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postprandial target is <180 mg/dL.[5] The AACE recommends even stricter glycemic control, with an A1C target of <6.5%, a preprandial target of ≤110 mg/dL, and peak postprandial glycemic target of ≤140 mg/dL.[6] In clinical practice, it is best to aim for glycemic targets that are as close to ADA or AACE guidelines as possible, provided one can do so safely. In doing so, the clinician must recognize that glycemic goals should be individualized, to take into account the presence of comorbid conditions and the expected longevity of the patient.[7]

Glycemic control in type 2 diabetes. Diet, exercise, weight loss, and adoption of a healthy lifestyle are the cornerstones of care for patients at all stages of diabetes. As the disease progresses, most patients with diabetes will also require pharmacologic therapy that will need to be intensified over time.[8]

Oral agents are the place to begin. Typically, pharmacologic management of diabetes begins with oral agents.[8] Several categories of oral medication can be used to treat type 2 diabetes, and more than 1 agent may be used for initial treatment of hyperglycemia. Insulin secretagogues (sulfonylureas and meglitinide analogs) are prescribed to treat the insulin secretory defect, whereas insulin sensitizers (metformin and thiazolidinediones) are used to address insulin resistance. Other agents include a-glucosidase inhibitors, which benefit patients with type 2 diabetes by slowing carbohydrate absorption, while glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors increase incretin levels, enhance insulin secretion in a glucose-dependent manner, and suppress pancreatic glucagon secretion.

In clinical practice, insulin therapy is often delayed because of misconceptions and fears about disease progression and the role of insulin.

When adding insulin becomes necessary

Even when combinations of these medications are used, many patients ultimately require the addition of exogenous insulin to achieve glycemic control.[9] In clinical practice, however, insulin therapy is often delayed because physicians and patients alike are prey to misconceptions and fears about disease progression and the role of insulin.[10] **TABLE 1** presents some of the most common preconceptions held by patients about the initiation of insulin therapy, and suggests strategies for overcoming each of them.[11]

To help guide your decision making, you can follow the AACE/ACE Diabetes Algorithm for Glycemic Control, an updated guide for moving from oral medications to insulin therapy, depending on A1C levels. The algorithm is available at www.aace.com/pub/pdf/GlycemicControlAlgorithmPPT.pdf.[12]

Early insulin gets results

Studies have demonstrated that the early use of intensive insulin improves beta-cell function and may enable patients to temporarily stop pharmacologic therapy for variable periods of time.[13-15] In a Canadian study, 405 patients with type 2 diabetes receiving 0, 1, or 2 oral agents and with A1C levels between 7.5% and 11.0% were randomized to either a basal insulin or intensification of oral agents without adding insulin.[16] Patients who were treated with insulin were 1.68 times more likely to achieve 2 consecutive A1C levels of 6.5% or less and achieved this endpoint sooner than those randomized to intensification of oral agents. Additionally, patients treated with insulin were able to achieve an adjusted mean A1C of 6.96%, compared with the 7.24% achieved by patients treated only with oral therapy. In addition to its glycemic benefits, insulin has also been shown to inhibit atherogenesis and improve triglyceride and high-density lipoprotein cholesterol levels.[17,18]

The next step: Choosing the best insulin regimen

Long-acting basal insulin. Insulin glargine and insulin detemir are long-acting insulin analogs that were developed to approximate normal basal pancreatic secretion.[19] Insulin glargine has a smooth, time-action pharmacokinetic profile without pronounced peaks.[20] Several studies indicate that once-daily insulin glargine is as effective as twice-daily neutral protamine Hagedorn (NPH) insulin in controlling hyperglycemia, and is associated with reduced nocturnal hypoglycemia.[20,21] Insulin detemir has also been shown to provide effective glycemic control with a re-

TABLE 1

"Insulin will make me fat," and other patient concerns you'll need to overcome

Patient concern	How you can respond
Fear: "I'm afraid of needles."	Insulin pens and smaller, thinner needles make injections almost painless.
Failure: "Going on insulin proves I can't take control of my disease."	The natural course of diabetes is to worsen over time, but controlling your blood glucose levels with insulin can slow that process down.
Stigma: "If people see me taking an insulin shot, they'll think I'm a sick person."	New injection devices like insulin pens are not very noticeable, and the needles are smaller and thinner than they used to be.
Weight gain: "Insulin will make me fat."	I'll help you find a nutritionist who can teach you how to eat healthier foods and develop an active lifestyle that helps keep you trim. And insulin is no more likely to make you fat than some of the oral agents you've been using.
Hypoglycemia: "I've heard that diabetics who use insulin can pass out suddenly, or even go into a coma. I think it's called hypoglycemia, and it scares me."	That's less likely to happen with the newer forms of insulin we use now. And if you do have a hypoglycemic episode, it will probably be something mild you can treat yourself. I can teach you how to recognize what's happening and what to do about it.
Complexity: "It all sounds too difficult for me to manage on my own."	We have new, step-by-step instructions you can follow when you start insulin therapy and when you need to make changes.
Complications: "I know people on insulin who have serious complications like heart attacks and kidney disease. Will that happen to me?"	Diabetes-related complications are the result of inadequate control of blood sugar levels. Insulin provides more intensive glycemic control than you've been achieving, and that helps avoid the complications you're concerned about. That's why I recommend you start using insulin.

Source: Brunton S, et al. The role of basal insulin in type 2 diabetes management. *J Fam Pract*. 2005.[11]

duced risk of hypoglycemia compared with NPH.[22] This long-acting basal insulin is approved for once- or twice-daily subcutaneous administration and, like glargine, exhibits a dose-dependent duration of action of up to 24 hours.[22,23]

Prandial insulin may also be needed. If basal insulin plus antidiabetic drugs are not sufficient to control hyperglycemia, you can add prandial insulin to the treatment regimen. For guidance on initiating and advancing insulin therapy, consult the consensus algorithm from the ADA and the European Association for the Study of Diabetes at http://care.diabetesjournals.org/content/32/1/193.full.pdf+html.[8] (See Figure 1 on page 198 of the pdf.) The rapid-acting insulin analogs—insulins aspart, lispro, and glulisine—have a more rapid onset and shorter duration of action than regular human insulin.[24] The pharmacokinetic profiles of rapid-acting insulin analogs more closely resemble the prandial insulin response seen in individuals without diabetes.[25] Rapid-acting analogs have an onset of action of 5 to 15 minutes—approximately twice as fast as regular insulin—and a duration of action of 2 to 5 hours, which is shorter than regular insulin.[24-27] These attributes allow for greater dosing flexibility, as patients can inject insulin immediately before or after eating rather than having to inject regular insulin 30 to 45 minutes before the planned meal.[24]

Sometimes your patient needs to use both. Basal-prandial regimens, appropriate for all patients with type 1 diabetes, can also be used for some patients with newly diagnosed type 2 diabetes and for those who have not achieved glycemic targets with 1 or more oral agents or with prandial or premixed in-

sulin regimens. Start newly diagnosed type 2 patients on a basal-prandial regimen if they have severe, symptomatic hyperglycemia. Such patients often have an A1C >10.0% or a fasting plasma glucose (FPG) >250 mg/dL. Oral agents alone are unlikely to reduce the A1C or FPG to target in such patients, and should be considered only after the extreme hyperglycemia has been reduced with an intensive insulin regimen.[5]

Premixed combinations are simpler, but have a downside

Premixed insulin combines an intermediate-acting insulin with a short- or rapid-acting insulin in a single injection. Premixed insulins are available in fixed-dose ratios to provide both basal and prandial insulin replacement. In addition to premixed regular-NPH combinations, 3 premixed insulin analog formulations are currently available: biphasic insulin lispro mix 75/25 (75% NPH and 25% lispro), biphasic insulin lispro mix 50/50 (50% NPH and 50% lispro), and biphasic insulin aspart 70/30 (70% NPH and 30% aspart).[28]

Premixed insulin is usually administered twice daily, before breakfast and supper.[29] In some instances, a third injection at lunch is necessary to achieve glycemic goals.[30] These regimens require patients to adhere to a consistent meal schedule and carbohydrate intake to avoid prandial hypo- and hyperglycemia.[29]

The disadvantage of a premixed insulin regimen is that the prandial and basal insulin components cannot be dosed independently. For example, if a patient who takes 75/25 insulin at breakfast has low blood sugars after breakfast but good glucose control at lunchtime and in the afternoon, it is not possible to reduce the amount of short-acting insulin without also reducing the dose of the NPH. Changing the dose of 75/25 to eliminate post-breakfast hypoglycemia may cause hyperglycemia in the afternoon, because the NPH dose will also be reduced. Separate injections of basal and prandial insulin provide a more physiologic regimen.

A subanalysis from the AT.LANTUS study examined glycemic parameters and safety over 24 weeks in 686 patients who switched from premixed insulin to once-daily insulin glargine.[31] Patients were allowed to use oral agents as well, before and after the switch. After patients made the switch, A1C and FPG were significantly reduced, and the incidence of severe hypoglycemia was low. The addition of prandial insulin at 1 or more meals was associated with further improvements in glycemic control.[31]

To help guide your decision making, consider the AACE/ACE Diabetes Algorithm for Glycemic Control, an updated guide for moving from oral medications to insulin therapy.

A multifaceted, stepwise approach

Ideally, when a physician diagnoses a patient with diabetes, he or she has access to a diabetes care team that includes a dietitian or nutritionist, a certified diabetes nurse educator, a pharmacist, and an exercise physiologist. The team's job is to educate the patient about the natural history of the disease and its complications and to teach diabetes self-management.

The real world. In practice, family physicians rarely have access to the kind of comprehensive diabetes care team that exists in specialty centers. You and your staff will need to provide the patient education that diabetes care requires, supplying patient-education handouts from online and print sources and making time to discuss food choices, meal planning, and daily exercise goals in follow-up visits. Written food and exercise logs are useful tools in this educational process.

Diabetes 101. At the time of diagnosis or at an early follow-up visit, be sure to inform the patient about all the treatment options—including insulin—that are available to treat the disease. Whenever possible, the discussion of insulin therapy should begin months or years before there is a need to initiate insulin treatment, so that when the time comes to start insulin, the patient will be more likely to accept the regimen. Patient education should include an introduction to carbohydrate content of different foods and the general principles of carbohydrate counting, home glucose monitoring, hypoglycemia awareness, and options for insulin delivery (syringe vs pen device).

When the time comes

To recognize the proper time to introduce insulin, evaluate A1C levels at least twice a year in patients who are meeting their glucose goals and every 3 months in those who

are not meeting goals or whose treatment regimen has been changed.[5] Additionally, patients should monitor their fasting, preprandial, and postprandial glucose levels regularly to be sure they are meeting glycemic targets and to minimize the risk of hypoglycemia. Glucose readings should be reviewed at every office visit.

Monitor glucose before and after meals

Both pre- and postprandial glucose levels should be monitored and managed in all patients with diabetes, whether or not they are treated with insulin. Some studies have suggested that home glucose monitoring may not improve glycemic control for patients taking oral agents. It is our view, however, that home glucose monitoring can facilitate changes in diet or exercise patterns and help physicians adjust or add treatment, based on pre- and postprandial glucose concentrations.

For some patients, focusing treatment initially on preprandial glucose may be sufficient, because elevated baseline preprandial glucose levels can lead to a higher overall plasma glucose profile and higher postprandial excursion.[32] Basal insulin can be used to lower the fasting glucose levels and the overall glycemic profile for those patients.

Other patients, however, may have normal fasting and preprandial blood glucose levels with postprandial hyperglycemia. For these patients, modest postprandial glycemic excursions may be decreased initially by lowering the overall glycemic profile with basal insulin. In some cases, an injection of rapid-acting insulin before the meals that are associated with postprandial hyperglycemia is an effective treatment option.

Both pre- and postprandial glucose concentrations contribute to the A1C. At higher A1C concentrations (>7.5%) fasting glucose contributes more than postprandial glucose to the A1C. Below this concentration, the reverse holds true.[33] As diabetes progresses, basal insulin can become insufficient to achieve glycemic control, and many patients eventually require the addition of prandial insulin at appropriate meals to control postprandial glucose excursions.[32]

The benefits of insulin treatment are most robust when both preprandial and postprandial glucose levels are taken into account. In a person with normal glucose homeostasis, about half the insulin released in a day is for basal regulation and the other half is meal related.[34] Thus, most insulin treatment regimens are designed to provide approximately 50% of insulin as basal coverage and 50% at meals.[34] Basal insulin suppresses gluconeogenesis between meals and overnight, whereas prandial insulin covers increases in blood glucose levels after meals.[34]

Use titration algorithms to balance glucose levels

Several simple titration algorithms can be used to initiate basal insulin. An initial dosage of 10 units daily (or 0.1 unit/kg) is a reasonable starting point for many patients with type 2 diabetes and moderate insulin resistance. This dose can be increased every 3 to 5 days until the target preprandial glucose level is achieved (**TABLE 2**).[35,36] If a basal-prandial insulin regimen is started, then typically half the 24-hour insulin dosage is given as basal insulin.[34] The remaining 50% is given as a rapid-acting insulin analog at meals. Dosages should be adjusted according to the patient's self-monitored blood glucose values.[35]

Prandial insulin therapy is often initiated with a single injection administered either at the largest meal of the day or at the meal that most often increases postprandial glucose above target levels. The dose of prandial insulin is ideally based on the carbohydrate content of the meal and the pre-meal blood sugar, but for patients whose meals do not vary much in terms of carbohydrate content, it may be simpler to give fixed mealtime doses. Additional injections are added at other meals as necessary.

A patient's 24-hour insulin dosage requirement can be estimated by multiplying the body weight (in kilograms) by a factor that takes the patient's presumed insulin sensitivity into account. One strategy is to use a factor of 0.3 if the patient is insulin sensitive (usually lean), 0.5 if the patient is of average sensitivity (average weight to moderately overweight), and 0.6 if the patient is relatively insulin resistant (obese or morbidly obese).[34] The total 24-hour insulin dose is the sum of

To recognize the proper time to introduce insulin, evaluate A1C levels every 3 months in patients who are not meeting their glucose goals, or whose treatment regimen has been changed.

TABLE 2

Weekly insulin titration schedule

Continue oral agent(s) at same dosage (eventually reduce)
Initiate insulin therapy If postprandial glucose levels are >140 mg/dL, add single insulin dose (about 10 U) in the evening. You can use: • NPH at bedtime, or • Insulin glargine at bedtime or morning, or • Insulin detemir at bedtime or both morning and evening if needed to reach goals.[36] If post-dinner glucose >180 mg/dL, consider premixed 70/30 or 75/25 insulin before dinner.
Increase insulin dose every 3 to 5 days as needed, provided no nocturnal hypoglycemia occurs. Increase to: • 2 U if FBG >120 mg/dL • 4 U if FBG >140 mg/dL • 6 U if FBG >160 mg/dL
Treat to target level (usually FBG <120 mg/dL)

FBG, fasting blood glucose; NPH, neutral protamine Hagedorn.

Source: Chan JL et al. *Mayo Clinic Proc.* 2003.[35] Adapted with permission.

The newer insulin analogs are more expensive than older formulations, but they more closely approximate physiologic insulin secretion.

the basal and prandial doses. It is crucial to take into account the oral agents a patient is using when calculating the total daily insulin requirements. In particular, patients who use insulin secretagogues may require less insulin if these medications are not stopped or reduced.

The effectiveness of a simple titration regimen was demonstrated in a study by Bergenstal and colleagues.[37] They compared outcomes for patients with type 2 diabetes who calculated their dosage of a prandial, rapid-acting insulin analog (insulin glulisine) using a simple titration regimen with patients who based their dosage on carbohydrate counting. Carbohydrate counting involves adding the amount of carbohydrates in all the foods for a given meal and then dosing prandial insulin according to a ratio of units of insulin per gram of carbohydrate. For example, a meal containing 60 g of carbohydrate requires 6 units of insulin if a patient uses 1 unit of insulin per 10 g of carbohydrate. Patients on the simple regimen adjusted their weekly mealtime insulin dose by 1, 2, or 3 units, depending on their pre-meal glucose patterns.

When the 2 groups were compared, patients using a simple dosing algorithm did as well as those who based their dosage on carbohydrate counting. They achieved a similar degree of glycemic control (A1C reduction= ~1.5%) and experienced fewer episodes of symptomatic hypoglycemia (defined as <50 mg/dL), 4.9 vs 8.0 events per patient year; P=.02).[37] These findings support the use of a simple alternative method for prandial-dose titration and may allay concerns that basal-prandial insulin regimens are complicated and tedious to implement.

The recently published 4T study evaluated different insulin regimens for patients not achieving therapeutic goal on oral agents. Patients were started on basal insulin, prandial insulin, or premixed insulin. After 1 year, the insulin regimen was intensified in those who were still not achieving therapeutic goals, and the patients were evaluated after another 2 years. Prandial insulin was added for patients initially treated with basal insulin if they were not at A1C goal, basal insulin was added for those who started with prandial insulin, and a dose of rapid-acting insulin was given at lunch to those on twice-daily premixed insulin who were not at goal. The A1C levels achieved at the end of the study did not differ among the treatment groups, and ranged from 6.8% to 7.1%.[38]

Overcoming reluctance

Despite convincing evidence that effective

glycemic control can help delay or prevent diabetic complications, more than half the patients with type 2 diabetes do not achieve the treatment goal of A1C below 7.0%.[39] Insulin therapy can help these patients reach glycemic targets rapidly and safely, but many patients and physicians are reluctant to start insulin for a variety of reasons.

For many, concern about hypoglycemia is at the top of the list. The way to address that concern is by educating patients to recognize symptoms of hypoglycemia and emphasizing the importance of frequent blood sugar monitoring, especially before driving and exercising. Insulin therapy does not increase the risk of hypoglycemic episodes. In fact, the risk of severe hypoglycemia in a patient with type 2 diabetes who has normal renal function and takes an appropriate dose of insulin is low.

Cost can also be a factor in the reluctance to start insulin therapy. The newer insulin analogs are more expensive than older formulations, but they more closely approximate physiologic insulin secretion and their use is associated with a reduced risk of hypoglycemia.

Finally, the perception that insulin regimens are complex and difficult to self-titrate is another common reason that physicians and patients are reluctant to begin insulin therapy or to progress from basal to basal/prandial regimens. In fact, insulin regimens are less complicated than patients fear. Several simple and practical algorithms are available to guide patients through a step-by-step process of initiating and advancing insulin therapy. Patients using these guidelines quickly become comfortable with insulin administration and savvy about interpreting blood glucose patterns based on meal content and exercise. Basal, premixed, and basal/prandial insulin regimens are all strategies that can help patients achieve their glycemic goals quickly and safely. JFP

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The risk of severe hypoglycemia in a patient with type 2 diabetes who has normal renal function and takes an appropriate dose of insulin is low.

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