

Overcoming Psychological Barriers to Insulin Use in Type 2 Diabetes

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Type 2 diabetes mellitus (DM) is characterized by a gradual decrease in insulin sensitivity in peripheral tissues and the liver (insulin resistance), followed by a gradual decline in β -cell function and insulin secretion. Given this decline, many patients with type 2 DM will require insulin therapy to achieve the glycemic target recommended by the American Diabetes Association of glycosylated hemoglobin (A1C) <7%. The combination of insulin plus oral antidiabetic drugs (OADs) has been shown to improve A1C values in patients who were not adequately controlled with OADs alone. Despite its established benefits, however, insulin therapy continues to be underused. The reluctance to initiate insulin therapy is often related to both provider and patient misperceptions about insulin's efficacy and side effects, as well as the perceived complexity of the treatment regimen. In addition, insulin therapy may be viewed as a "last resort" treatment option for severe disease or as "punishment" for patients' failure to manage their disease. However, patients should be made aware from the time of diagnosis that diabetes is a progressive disease and that it is likely that insulin therapy will be required at some point during the course of the disease. The subject of insulin therapy, therefore, should be approached positively and should be presented as an effective and flexible way to achieve glycemic goals for any patient at any time during therapy. (*Clinical Cornerstone*. 2006;8[Suppl 2]:S19–S26) Copyright © 2006 Excerpta Medica, Inc.

Type 2 diabetes mellitus (DM) is characterized by a gradual decrease in insulin sensitivity in peripheral tissues and the liver (insulin resistance), followed by a gradual decline in β -cell function and insulin secretion. At diagnosis, β -cell function in patients with type 2 DM may be significantly diminished—newly diagnosed patients in the United Kingdom Prospective Diabetes Study (UKPDS) had only 50% of normal β -cell function.¹ After 6 years, endogenous insulin secretion was <25% of normal.¹ Thus, a patient living with type 2 DM for 12 years may be as insulin-deficient as a patient with type 1 DM.

Given this inevitable decline in β -cell function and insulin secretion, most patients with type 2 DM will require insulin therapy to achieve the glycemic target recommended by the American Diabetes Association (ADA) of glycosylated hemoglobin (A1C) <7%.² The

combination of insulin plus oral antidiabetic drugs (OADs) has been shown to improve A1C values in patients who were not adequately controlled with OADs alone.³ A substudy of the UKPDS demonstrated that early addition of insulin to OAD therapy can safely maintain A1C near target levels in the first 6 years after diagnosis.⁴ Insulin therapy also has been shown to improve insulin sensitivity and, in some cases, to reverse insulin resistance.^{5–8} The availability of newer long-acting basal insulins and rapid-acting insulin analogues that are associated with lower rates of hypoglycemia has made insulin therapy a more attractive choice for patients with type 2 DM.

Despite its established benefits, however, insulin therapy continues to be underused in the United States.⁵ Physicians are reluctant to prescribe insulin therapy

KEY POINT

Most patients with type 2 DM will require insulin therapy to achieve the ADA-recommended glycemic target of A1C <7%.

despite ample evidence that OAD monotherapy is unlikely to maintain glycemic control over time. Koro et al⁹ found that use of insulin actually declined from 24% in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) to 16% in NHANES (1999–2000), while use of OAD monotherapy increased. Reluctance to initiate insulin therapy is also common in other countries. In a study of attitudes toward insulin therapy among health care providers in 13 countries, Peyrot et al¹⁰ found that 55% of nurses and general practitioners would delay insulin therapy until absolutely necessary. Additionally, general practitioners tended to be more reluctant to use insulin therapy compared with diabetologists and endocrinologists.^{5,10} Among specialists, the overall approach to managing diabetes involves individualized treatment, use of combination therapy, and frequent use of insulin; however, among primary care physicians, this treatment pattern is not seen as commonly.⁵

The reluctance to initiate insulin therapy may be related to both the provider and the patient. Health care providers may not initiate insulin therapy because of the difficulty and time involved in educating the patient, the potential for metabolic complications such as hypoglycemia and weight gain, and the perception that insulin increases cardiovascular risk. Additionally, they may believe that patients will not be able to adhere to complex insulin regimens. Patients also have concerns about starting insulin—they may believe that their condition has become more severe and that insulin is now required because of a personal failure to adhere to other treatment regimens. They may fear that insulin therapy will severely restrict their personal lives and be too complex for them to manage. They may relate a family member's diabetes complications (eg, amputation, vision loss) to insulin therapy rather than insufficient glycemic control. Patients may also be uncomfortable with the prospect of daily injections.

This paper explores the concerns that contribute to the reluctance to initiate insulin therapy from the perspective

of both the health care provider and the patient and suggests ways to overcome these barriers to achieving optimal glycemic control.

THE PROVIDER'S PERSPECTIVE

Concerns About the Efficacy of Insulin in Type 2 Diabetes

There may be a perception among some primary care physicians that insulin is not effective in the treatment of type 2 DM. In a 1997 study by Hayward et al,¹¹ patients who started insulin therapy had a mean reduction of only 0.9% after 1 year; at 2 years, A1C was still >8% in 60% of study participants. Patients with a baseline A1C of 13% had a 3-fold greater reduction than those who had a baseline A1C of 9%. The authors concluded that insulin was safe and effective in achieving moderate glycemic control in patients with poor control, but it was rarely effective in achieving tight glycemic control.

Since the publication of that study, several new formulations of insulin and new insulin regimens have been developed. These newer approaches to insulin therapy have been demonstrated in controlled clinical trials to be effective in achieving ADA-recommended glycemic targets. One such approach is the addition of a basal insulin to an OAD treatment regimen. Basal insulin suppresses glucose production between meals and overnight and remains at nearly constant levels (**Figure 1**),^{3,12} while OADs cover postprandial insulin needs.

In the Treat-to-Target Trial,¹² a randomized, open-label, parallel-group, 24-week, multicenter study, 756 overweight men and women with inadequate glycemic control (A1C 7.5%–10%) were randomized to receive bedtime glargine or neutral protamine Hagedorn (NPH) insulin QD while continuing their OAD regimen (metformin + sulfonylurea). At the end of the study, ~60% of patients in both groups achieved the A1C target of ≤7%. Mean A1C was similar in both groups (glargine, 6.96% vs NPH, 6.97%).

In a 24-week, open-label, parallel-group, multicenter trial,¹³ the addition of basal insulin to OAD therapy was shown to be more effective than an insulin-only BID regimen. In this study, 371 insulin-naïve patients with poor glycemic control (A1C 7.5%–10.5%) on a sulfonylurea plus metformin regimen were randomly assigned to receive insulin glargine plus glimepiride and metformin, or 70% human/30% regular (70/30) NPH insulin BID with no oral medication. Patients who were treated with glargine plus OADs achieved better glycemic control

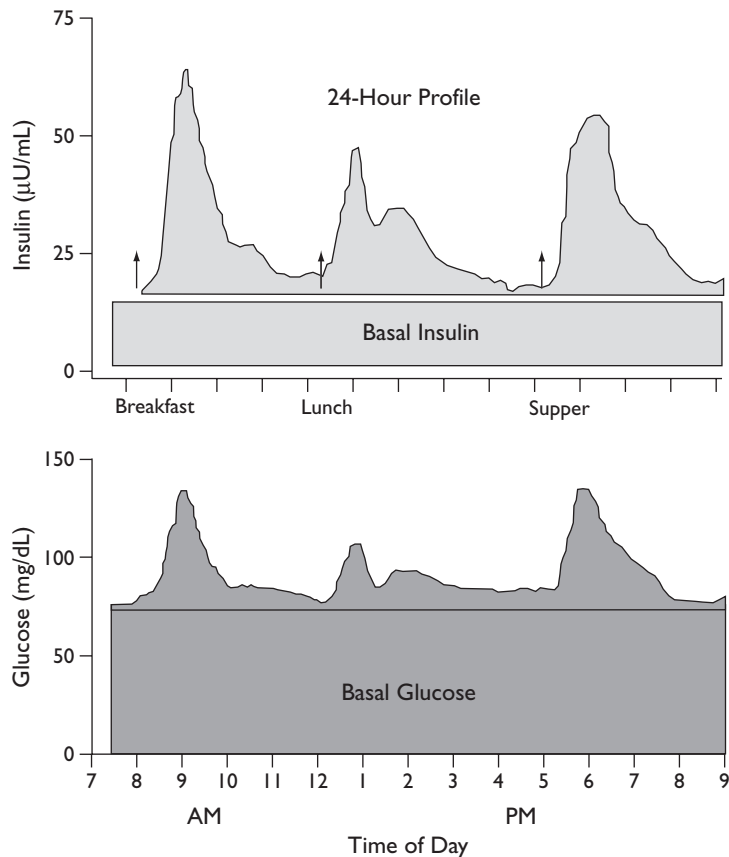


Figure 1. Basal-bolus insulin therapy more effectively mimics natural insulin secretion. Basal-bolus insulin suppresses glucose production between meals and overnight and keeps insulin at nearly constant levels.^{3,12} Reprinted with permission from The Diabetes Consortium, Inc.

than those who were treated with the NPH insulin BID. Mean reduction in A1C from baseline was significantly greater in the glargine group (-1.64% vs -1.31% , $P < 0.001$), and a significantly higher percentage of these patients reached the A1C target of $\leq 7.0\%$ without confirmed nocturnal hypoglycemia (45.5% vs 28.6% , $P < 0.001$). Additionally, the decrease in fasting plasma glucose (FPG) levels was greater in patients treated with glargine plus OADs, and a significantly higher percentage of these patients reached the ADA-recommended FPG target of ≤ 100 mg/dL (31.6% vs 15.0% , $P < 0.001$).

Results of these and other trials of the newer insulin formulations confirm the efficacy of insulin therapy in achieving tight glycemic control. It is important to note that in the Treat-to-Target and multicenter trials just discussed, OADs were aggressively titrated to achieve FPG and A1C targets. Therefore, an uncompromising commitment to treating to target is essential for achieving optimal outcomes with OADs plus insulin.

KEY POINT

An uncompromising commitment to treating to target is essential for achieving optimal outcomes with OADs plus insulin.

Concerns About Hypoglycemia

The fear of hypoglycemia is a genuine concern and probably the main barrier to health care providers initiating insulin therapy. Compared with the rate of hypoglycemia in patients with type 1 DM, however, the annual rate of serious hypoglycemia (episodes requiring medical intervention or the help of another person) in patients with type 2 DM is relatively low (2% – 3%).¹⁴ Additionally, the newer longer-acting and once-daily basal insulin formulations appear to be associated with lower rates

of hypoglycemia than the formulations that are administered more frequently.

In the Treat-to-Target Trial discussed previously,¹² intermediate-acting NPH insulin and long-acting insulin glargine were not significantly different with respect to efficacy (ie, lowering A1C levels). However, insulin glargine was associated with lower rates of documented nocturnal hypoglycemia and other categories of symptomatic hypoglycemia. In addition, 25% more patients receiving glargine achieved the target A1C without documented nocturnal hypoglycemia. In another study comparing 70% protaminated insulin/30% biphasic insulin aspart (BIAsp 70/30) BID with insulin glargine in patients with type 2 DM, the rate of minor hypoglycemic episodes was nearly 3 times higher among patients receiving BIAsp 70/30.¹⁵ Other studies have confirmed the lower incidence of nocturnal hypoglycemia with insulin glargine compared with 70/30 NPH insulin.^{13,16} Because fear of hypoglycemia is a major obstacle to the use of insulin, the availability of newer insulin formulations with improved 24-hour time-action profiles should help alleviate these concerns.

For patients who do not achieve adequate glycemic control with a basal insulin plus OADs, the newer rapid-acting insulin analogues (eg, aspart, glulisine, lispro) can

be used instead of OADs, as these insulin formulations better mimic the action of endogenous insulin (**Figure 2**).^{17,18} Aspart and lispro have a shorter time to peak effect compared with regular insulin, but more importantly, their duration of action is shorter (~3 hours vs 6–7 hours). This results in less sustained insulin action between meals and, therefore, a lower risk of hypoglycemia.

When initiating insulin therapy, however, it is imperative that patients be educated about the importance of self-monitoring of blood glucose (SMBG). SMBG allows patients to determine when glucose concentrations are approaching hypoglycemic levels so that a hypoglycemic episode can be avoided.

Concerns About Weight Gain

Weight gain associated with insulin therapy is a serious concern among providers,¹⁹ as weight gain in patients who are already obese can lead to further insulin resistance and poor glycemic control. Significant weight gain is more common with split-dose insulin regimens compared with once-daily formulations. In a 28-week, parallel-group study,¹⁵ 233 insulin-naïve patients with type 2 DM who were poorly controlled on metformin alone or in combination with other OADs were randomly assigned to treatment with BIAsp 70/30 BID or insulin glargine at

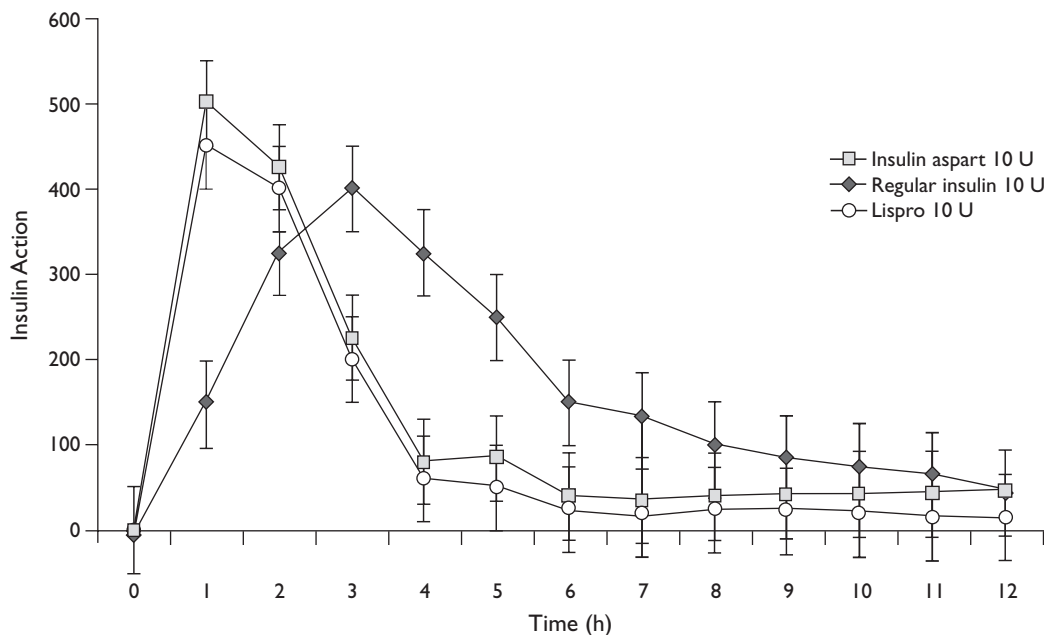


Figure 2. Rapid-acting insulin analogues (eg, aspart, lispro) better mimic the action of endogenous insulin. Aspart and lispro have a shorter time to peak effect than regular insulin, and their duration of action is shorter (~3 hours vs 6–7 hours), resulting in less sustained insulin action between meals and, therefore, a lower risk of hypoglycemia.^{17,18} Reprinted with permission from The Diabetes Consortium, Inc.

bedtime. Mean (SD) weight gain was significantly greater in the group treated with BIAsp 70/30 BID (5.4 [4.8] kg vs 3.5 [4.5] kg, $P < 0.01$). In the UKPDS study,¹ the mean weight gain in the primary study population was ~9 pounds. However, the addition of metformin to insulin therapy has been found to attenuate weight gain.^{20,21} In a randomized controlled trial of 96 patients, those receiving bedtime insulin plus metformin experienced no change in weight (mean [SD] change, 0.9 [1.2] kg), whereas those receiving bedtime insulin plus glyburide, glyburide and metformin, or an additional dose of insulin in the morning, experienced significant weight gain (3.9 [0.7] kg, 3.6 [1.2] kg, 4.6 [1.0] kg, respectively; $P < 0.001$ vs insulin plus metformin).²⁰ In a second trial, the addition of metformin to insulin improved glycemic control, lowered insulin requirements by almost 30%, and attenuated the weight gain associated with insulin therapy alone.²¹

Hypoglycemia between meals may lead patients to compensate by eating frequent snacks, which can augment insulin-associated weight gain. It follows then that insulin formulations associated with lower rates of hypoglycemia may reduce the likelihood of weight gain due to eating between meals. Bedtime administration of insulin can help avoid this type of weight gain. The use of OADs plus once-daily basal insulin at bedtime is also associated with less weight gain than combination therapy with premixed BID insulin formulations. Moreover, patients with type 2 DM are advised to be on strict diet and exercise regimens, which can help mitigate the effects of insulin on body weight.

Concerns About Cardiovascular Effects with Insulin Therapy

An additional concern among physicians is that insulin may increase cardiovascular risk. However, evidence from the UKPDS demonstrates that intensive blood glucose control with sulfonylureas or insulin significantly reduces the risk of microvascular complications ($P < 0.001$).²² In the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study,^{23–25} there was a significant reduction in mortality in diabetic patients who had had an acute myocardial infarction and received intensive insulin treatment compared with those who had not received intensive treatment ($P = 0.027$ at 1 year; $P = 0.011$ at mean follow-up of 3.4 years). In a study by van den Berghe et al,²⁶ inten-

sive insulin treatment in critically ill patients (including patients without diabetes) reduced mortality during intensive care, as well as overall mortality. None of the available evidence supports the idea that insulin may be cardiotoxic.

Concerns About Patient Adherence to Complex Regimens

Physicians may fear that their patients will not be able to adhere to complex insulin regimens and, therefore, may delay insulin therapy. However, the newer insulin regimens and the injection pens that are currently available can reduce the complexity of insulin therapy. As discussed, adding a basal insulin at bedtime while continuing OAD therapy has been shown to be an effective approach to achieving glycemic control. The advantage of this regimen is that patients can administer insulin conveniently at bedtime, minimizing the impact on their daily activities. Insulin pens can simplify therapeutic regimens for patients since these devices have a disposable needle and an insulin cartridge that contains a premeasured insulin dose, making injection more accurate and less cumbersome.²⁷

Physicians also may be reluctant to teach patients diabetes self-management techniques, especially insulin therapy, as this can be a formidable and time-consuming task. Their reluctance can lead to a delay in initiating insulin therapy; however, certified diabetes educators are a valuable asset to busy physicians. Diabetes educators can help patients manage their disease, including the complexities of insulin therapy.

KEY POINT

Diabetes educators can help patients manage their disease, including the complexities of insulin therapy.

THE PATIENT'S PERSPECTIVE

Concerns About Insulin as the “Last Resort”

Once insulin therapy is prescribed, patients may believe that their diabetes has become more severe or that they have personally failed to control the disease with the prescribed treatment regimen.^{27–29} This perception may be a result of their physician's approach to the subject of insulin. For example, patients may receive subtle mes-

sages that insulin is the “last resort” in treatment options or that insulin will have to be initiated if the patient fails to control the disease with diet, exercise, and oral medication. Thus, patients may view insulin therapy as a “threat” or as a “punishment” for their personal failure.

Yet the subject of insulin therapy should be approached positively. In fact, the possibility of insulin therapy should be discussed from the time of diagnosis. Patients must be made aware that diabetes is a progressive disease characterized by gradually declining β -cell function and insulin secretion and gradually increasing insulin resistance, and that the eventual need for exogenous insulin is likely. Insulin therapy should be presented as an effective way to replace the body’s insulin at any time during the course of therapy to help patients achieve their glycemic goals. Achieving glycemic goals and bringing their insulin levels into balance will help patients not only feel better but also feel that they have better control of their disease. Insulin therapy may also provide flexibility for patients who have difficulty controlling their daily diet and exercise patterns (eg, frequent travelers). Insulin therapy should never be presented as a “last resort” or as “punishment” for a patient’s inability to control their disease.

KEY POINT

The subject of insulin therapy should be approached positively and should be discussed from the time of diagnosis.

Concerns About the Complexity of the Insulin Regimen

Insulin therapy can seem overwhelming for some patients when they are faced with the prospect of determining dosages, handling syringes and vials, and administering insulin at specific times, in addition to the demands of glucose monitoring. However, patients should be reassured that a basal insulin regimen is easy to manage and that this insulin formulation can be administered at bedtime so as not to complicate their daily activities. Treatment regimens should also be individualized, taking into account a patient’s schedule and routine. Certified diabetes educators can assist patients in

learning about insulin administration and SMBG, and they can reinforce the importance of following a comprehensive treatment regimen, including diet and exercise plans and pharmacologic treatment.

Concerns About Daily Injections

Injection-related anxiety is one of the most common reasons for patient resistance to starting insulin therapy.²⁹ Patients should be reassured that the ultrafine needles currently used are smaller, thinner, and coated so as to lessen pain on injection. Patients should also be informed about insulin pens. Although insulin pens contain a needle that needs to be attached to the pen, the needle is very small, and the device does not resemble a syringe. These characteristics may help to allay patients’ fears about needles and make the need for daily injection psychologically more acceptable.

Insulin pumps are also available for patients who have a serious fear of needles or for those who may not have the dexterity required to manage a needle or pen. These devices deliver a continuous measured dose of insulin via a catheter inserted through the skin. The pumps can also be programmed to release extra insulin before each meal.²⁷ However, pumps are best used by highly motivated patients or caregivers who can handle all aspects of pump use and care, as the catheter does need to be inserted into the skin and the pump needs to be maintained. Additionally, the patient or caregiver must be able to give an injection if the pump fails. For those patients whose injection anxiety may keep them from starting any type of insulin therapy, assistance from a behavior counselor who can employ desensitization techniques may be helpful.

CONCLUSIONS

Primary care physicians may be reluctant to start insulin therapy in patients with type 2 DM until it is absolutely necessary, and patients may view the initiation of insulin as a “last resort” treatment option for severe disease or as “punishment” for their failure to manage their disease. However, much of this resistance can be explained by misperceptions about insulin’s efficacy and side effects, as well as the perceived complexity of the treatment regimen. The availability and effectiveness of longer-acting, once-daily insulin formulations can help address many of these concerns. Once-daily insulin formulations combined with OADs have been shown in controlled clinical trials to achieve tight glycemic control in patients with

type 2 DM. The improved time-action profiles of these formulations provide a relatively constant level of plasma insulin, thereby reducing the incidence of hypoglycemia. In addition, combining once-daily insulin formulations, such as insulin glargine, with metformin can help attenuate the weight gain associated with insulin therapy. Once-daily bedtime administration of these formulations also simplifies the insulin regimen. Overcoming the psychological barriers to insulin use can help facilitate earlier and more aggressive intervention and therefore more optimal glycemic control in patients with type 2 DM.

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