

Empowering Patients During Insulin Initiation: A Real-World Approach

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Glycemic control is suboptimal in many patients with type 2 diabetes mellitus (T2DM). Despite documented benefits of insulin therapy, initiation of insulin is delayed in many cases because of the reluctance of patients and physicians to use this important treatment. A review of the literature revealed that educating patients about the role of insulin in managing T2DM and the advantages of using insulin analogs and insulin delivery devices may help alleviate some patients' concerns regarding insulin therapy. Compared with standard clinic-directed approaches, patient-driven algorithms that empower patients to initiate and titrate basal insulin therapy have been shown to improve glycemic control. Additional research is needed to confirm the importance of patient empowerment programs in T2DM management.

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The results of the 2005-2006 National Health and Nutrition Examination Survey¹ showed that 12.9% of adults aged 20 years or older in the United States have diabetes mellitus, though an estimated 40% of these cases have not been diagnosed. In addition, almost 30% of US adults have prediabetes (ie, impaired fasting glucose or impaired glucose tolerance),¹ placing them at elevated risk for type 2 diabetes mellitus (T2DM).²

Type 2 diabetes mellitus, which accounts for up to 95% of diabetes mellitus cases,² is a progressive disorder characterized by resistance to insulin-dependent glucose uptake and gradual β -cell failure. Inadequate glycemic control is associated with an elevated risk of vascular complications, which exact heavy personal and societal burdens. Individuals with diabetes mellitus are 2 to 4 times more likely to have a stroke and to die of

cardiovascular disease than those without diabetes mellitus.³ Diabetes mellitus also is the leading cause of blindness among individuals aged 20 to 74 years, and it accounts for an estimated 44% of new cases of kidney failure.³

Intensive management of hyperglycemia early in the course of diabetes mellitus is crucial to reduce risks of vascular complications. Researchers with the United Kingdom Prospective Diabetes Study (UKPDS)⁴ found that aggressive management with sulfonylureas or insulin to achieve a glycosylated hemoglobin (HbA_{1c}) value of 7% or less soon after T2DM diagnosis reduced patients' risk of microvascular events (eg, nephropathy, neuropathy, retinopathy) by 25% compared with conventional treatment ($P=.0099$).

Follow-up analysis of the UKPDS patients revealed compelling evidence of long-term benefits of early aggressive management.⁵ The difference in HbA_{1c} values between the aggressive and conventional treatment groups dissipated within 1 year of study cessation, and these values remained statistically similar over the 10-year follow-up period. Nevertheless, patients who received intensive therapy, compared with the other patients, showed statistically significant lower rates of microvascular events (relative risk reduction [RRR], 24%; $P=.001$); myocardial infarction (RRR, 15%; $P=.01$); any diabetes-related endpoint (RRR, 9%; $P=.04$); diabetes-related death (RRR, 17%; $P=.01$); and all-cause death (RRR, 13%; $P=.007$).⁵

These results demonstrate that delaying treatment intensification in individuals newly diagnosed with T2DM contributes to an avoidable risk of vascular complications. Yet, according to the National Committee for Quality Assurance, between 30% and 47% of patients with diabetes mellitus did not reach recommended HbA_{1c} goals in 2007.⁶ Other sources suggest that this percentage may be substantially higher.⁷

Patients and clinicians alike report that concerns about the complexities of insulin therapy limit insulin initiation and acceptance. However, results of clinical trials comparing patient-driven insulin titration algorithms with standard clinic-directed insulin titration algorithms suggest that blood glucose levels can be safely and effectively managed by patients.⁸⁻¹¹ These results also suggest that empowering patients with diabetes mellitus to make their own treatment choices often results in improved attitudes among those patients about their illness.

For the present clinical practice article, I conducted a review of literature in the National Library of Medicine's PubMed database to identify studies published between January 1980 and June 2009 that assessed the relationship between patient empowerment and glycemic control. The following

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key words were used in the search: *glycemic control, insulin, patient education, patient empowerment, and type 2 diabetes*. I discuss the importance of educating patients about insulin therapy and empowering them to manage their own disease. I also highlight tools that healthcare providers can use to facilitate successful self-management and to encourage the appropriate intensification of therapy in patients with T2DM.

Factors Delaying Treatment Intensification

To increase the number of patients who are placed on intensified regimens, it is important to understand factors that delay treatment intensification.

Providers

The American Diabetes Association (ADA)² and the American Association of Clinical Endocrinologists (AACE)¹² recommend that patients with diabetes mellitus maintain HbA_{1c} values of less than 7% and less than 6.5%, respectively. The reluctance of providers to intensify antidiabetes therapy is an avoidable factor contributing to low rates of achieving HbA_{1c} goals in the United States.¹³⁻¹⁵

In one prospective cohort study conducted in the primary care setting, researchers found that oral antiglycemic treatment was intensified in only 128 (22%) of 574 clinic visits of patients with hyperglycemia.¹⁶ In a similar study, at the end of 2 years, patients with diabetes mellitus who visited their healthcare providers quarterly—but did not have antiglycemic treatment intensified during the first 3 quarters of therapy—had HbA_{1c} values that were 1.4% higher than patients who had antiglycemic treatment intensified during that time.¹⁷

Insulin is the most effective glucose-lowering agent, as well as the most established antiglycemic therapy.¹⁸ However, physicians may be hesitant to use insulin therapy for a number of reasons. Initiating insulin therapy for patients whose glucose levels were formerly controlled with oral antidiabetes medications has been perceived by primary care practitioners as difficult—mainly because of the time necessary to implement this transition and the challenge in understanding the intricacies that surround newer insulin modalities and protocols.

Although certified diabetes educators (CDEs) can be a useful resource for providing diabetes self-management education (DSME) to patients initiating insulin and for facilitating the insulin initiation process, only one-third to one-half of patients with diabetes mellitus in the United States receive DSME.^{19,20} Barriers to the use of CDEs include lack of referrals by physicians, insufficient reimbursement for DSME by the Medicare program, and other logistical and financial obstacles.^{19,21}

In addition, uncertainty about insulin dosing may translate into clinical inertia and become a powerful barrier to initiating insulin therapy. Other factors that likely contribute to

delayed insulin use include the desire of physicians to avoid insulin injections and complex insulin regimens and the perceived risks of hypoglycemia and weight gain.^{13,15} Because T2DM is a progressive disease, clinical inertia may lead to initiation of insulin therapy only after patients have exhibited an unnecessarily lengthy history of poor glycemic control, resulting in the development of complications.²²

Patients

Data from clinical trials suggest that some delays in intensifying treatment may be attributed to patients' unwillingness to use insulin therapy. In the UKPDS,²³ more than one-quarter of patients assigned to insulin therapy refused treatment. Patients report a variety of reasons for avoiding insulin therapy, ranging from a misunderstanding of the clinical course of T2DM to injection avoidance.^{13,15}

Although physicians often attribute their own hesitancy in prescribing insulin to patient concerns, recent data suggest that a gap exists between the barriers to insulin use that physicians ascribe to their patients and the barriers actually reported by patients.¹⁵ A comparison of attitudes and beliefs of patients who started insulin therapy with those of patients who were hesitant to start insulin therapy revealed that patients in the latter group were less likely to believe that their illness was serious (47% patients using insulin, 7% patients not using insulin; $P<.001$); were more afraid of addiction to insulin (21% patients using insulin, 39% patients not using insulin; $P<.01$); and were more concerned about hypoglycemia (4% patients using insulin, 12% patients not using insulin; $P=.05$).¹⁵ By contrast, physicians attributed their hesitancy to initiate insulin therapy for patients who met standard criteria for insulin to the following: concerns about patient nonadherence to treatment (92%); patient fears of hypoglycemia (80%); concern that a patient would be unable to cope with pain associated with repeated blood tests (54%); and concern that a patient would be unable to cope with pain associated with repeated injections (48%).¹⁵

It is noteworthy that physicians inappropriately assigned more importance to patients' needle phobias than to patients' poor understanding of T2DM and insulin therapy.¹⁵

These results underscore the importance of educating physicians about the need to discuss concerns regarding initiating insulin therapy with each patient. In a survey of primary care physicians, most respondents agreed that their patients feel much better after initiating insulin therapy and that their patients were capable of managing the demands of insulin.²⁴ Advice about managing these demands can be among the most empowering pieces of information that physicians can communicate to patients.

Patient Empowerment in Insulin Therapy

A variety of factors can influence patients' attitudes toward insulin therapy. Interviewing patients regarding their underlying feelings about insulin may help primary care practi-

tioners identify individuals who are reluctant to use insulin. Such interviews may also help physicians address patients' concerns. Even in the absence of identified concerns, education and counseling about insulin can give patients the knowledge and confidence to accept and adhere to insulin therapy and to make effective self-management decisions based on their own priorities and goals.

Referring patients with T2DM to CDEs is another important strategy that can help patients learn about their disease. Data indicate that DSME provided by CDEs can enhance the health and well-being of patients with diabetes mellitus.²⁵⁻²⁷ Because of the complexity of some insulin regimens, DSME may be particularly useful for patients initiating insulin. Furthermore, by referring patients to CDEs, physicians may reduce their own need to provide education to candidates for insulin therapy.¹⁹

Reimbursement for DSME can be low. Receiving DSME in small groups may be more affordable for patients than receiving it in one-on-one settings.²¹

Role of Insulin in T2DM Management

Accumulating data suggest that many patients do not have an accurate understanding of the role of insulin in T2DM.^{13,15} For example, some patients equate insulin use with worsening T2DM, associating the development of its complications with the initiation of insulin therapy.^{13,15} These patients may conclude that insulin use is only for individuals who have personally failed to manage their disease. To address these concerns, healthcare providers must define the actual role of insulin in T2DM—preferably at the time of diagnosis and within the context of pathophysiologic mechanisms of the disease.

All patients diagnosed as having T2DM need to understand that T2DM is progressive—with insulin production decreasing over time—and that insulin “replacement” is required by most patients. Patients may need to be reassured that even if they adhere to a healthy lifestyle and medication regimens, the need for insulin is part of the ongoing disease progression rather than a sign of personal failure. Patients should also be made aware that day-to-day decisions regarding T2DM management are important in reducing risks of complications.

Treatment recommendations for initiating antidiabetes therapy in patients who are naive to therapy are based on HbA_{1c} values at time of diagnosis.^{2,12,18} Lifestyle modifications are essential for all patients and must be part of any treatment plan. For patients whose HbA_{1c} levels are 8% or less, drugs that lower hepatic glucose secretion (eg, metformin), improve insulin sensitivity (eg, thiazolidinediones), or increase endogenous production of insulin (eg, sulfonylureas, glinides, glucagon-like peptide 1 agonists) may be used alone or in combination to initiate treatment.^{2,12,18} However, these agents rely on β -cell function for efficacy. When β -cell function ceases, insulin therapy is required.

Basal insulin is recommended for consideration in patients with HbA_{1c} values greater than 7% and is the first-line treatment recommendation for patients with HbA_{1c} values of 10% or more.¹² Accumulating evidence suggests that β -cell failure occurs much earlier and is more severe than has been previously recognized.²⁸ In fact, individuals in the upper tertile of impaired glucose tolerance have already lost more than 80% of their β -cell function. Reviewing a timeline of the progression of T2DM (*Figure 1*) with patients can help clinicians and patients recognize the importance of early intensive intervention and determine whether insulin therapy may be appropriate.²⁹ By explaining that oral agents are ineffective if insulin is not being produced by the pancreas and that insulin therapy can address elevations in fasting blood glucose and postprandial blood glucose, clinicians can clarify the rationale for initiating insulin therapy sooner rather than later.

Insulin Analogs vs Human Insulins

The limitations of human insulin therapies may be largely responsible for unfavorable impressions of insulin use among patients. Regular human insulin (RHI) and neutral protamine Hagedorn (NPH)—two older human insulin therapies—have several drawbacks. For example, these therapies are associated with a relatively high risk of weight gain and hypoglycemia, they provide unpredictable insulin action, and they necessitate the use of inconvenient dosing schedules to replicate endogenous insulin secretion.^{30,31} Thus, reassuring patients about the benefits of newer insulin analogs may be advisable.

Two long-acting basal insulin analogs (detemir and glargine) and three rapid-acting insulin analogs (aspart, glulisine, and lispro) are more convenient to use and have fewer adverse effects than human insulin therapies. Insulin analogs are molecularly modified versions of human insulin designed with specific pharmacodynamic and pharmacokinetic properties that better approximate a naturally occurring insulin profile (*Figure 2*).^{30,32-35} The improved pharmacologic profiles of long-acting insulin analogs can allow for once-daily dosing.

Randomized controlled treat-to-target trials have demonstrated that long-acting insulin analogs reduce the risk of hypoglycemia and—particularly in the case of insulin detemir—reduce weight gain.^{30,32,36-39} For example, in a 24-week treat-to-target trial comparing insulin glargine with NPH, when each was added to treatment with oral agents, both therapies produced similar glycemic control.⁴⁰ However, insulin glargine was associated with lower rates of documented nocturnal and symptomatic hypoglycemia than NPH.⁴⁰ A meta-analysis of randomized controlled trials comparing insulin glargine with NPH showed that both agents resulted in similar improvements in fasting plasma glucose (FPG) and HbA_{1c}, though patients using insulin glargine reported fewer cases of hypoglycemia.⁴¹

Another treat-to-target study⁴² reported that insulin detemir and NPH provided similar glycemic control. However,

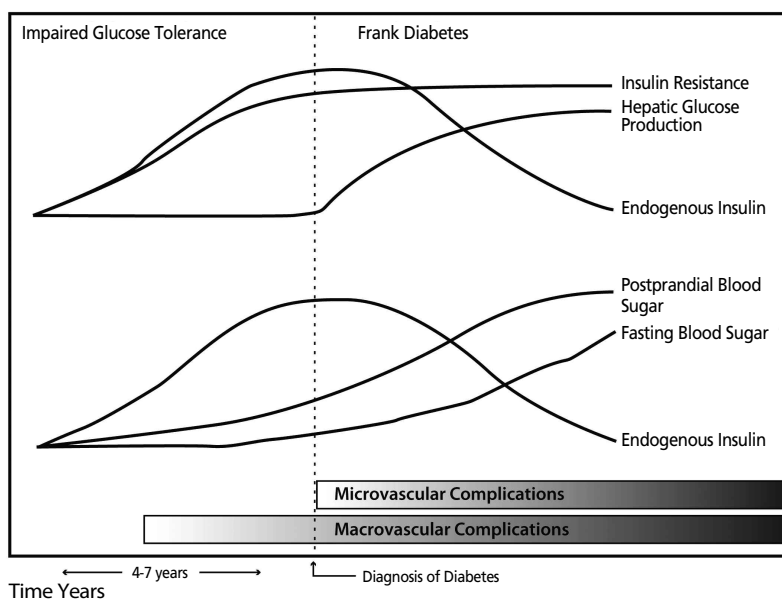


Figure 1. Timeline showing development of diabetes mellitus, illustrating insulin resistance and insulin deficiency. The top graph depicts effects of insulin resistance on endogenous insulin secretion. The bottom graph depicts effects of endogenous insulin deficiency on postprandial blood sugar and fasting blood sugar. From *Clinical Diabetes* by Ramlo-Halsted BA, Edelman SV.²⁹ Copyright 2000 by American Diabetes Association. Reproduced with permission of American Diabetes Association via Copyright Clearance Center.

patients using insulin detemir experienced less hypoglycemia and weight gain compared to patients using NPH. Trials comparing insulin detemir with insulin glargine have shown that both agents produce similar glycemic control, though insulin detemir is associated with less weight gain than insulin glargine.^{36,43}

Findings from treat-to-target trials investigating insulin detemir and insulin glargine have been confirmed in large, prospective, observational studies of the use of these agents in routine clinical practice.⁴⁴⁻⁴⁶ In the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE) study,^{44,45} patients with T2DM were prescribed insulin detemir as basal insulin. During 14 weeks of follow-up, HbA_{1c} levels in these patients decreased by 0.9%, and the incidence of major hypoglycemic events declined significantly, from 0.8 to 0.1 per patient-year ($P < .001$).⁴⁵ In a post hoc analysis of data from PREDICTIVE patients who were insulin-naïve at baseline, HbA_{1c} levels declined by 1.3% ($P < .001$), with low rates of any hypoglycemic episode (1.2 episodes per patient-year), nocturnal hypoglycemic episodes (0.3 episodes per patient-year), and serious hypoglycemic episodes (0 episodes per patient-year).⁴⁴

In a study of more than 12,000 patients with T2DM, the addition of insulin glargine to oral agents for 9 months resulted in a mean decrease of 1.7% in HbA_{1c} and a mean decrease of 71 mg/dL in fasting blood glucose levels.^{46,47} The incidence of hypoglycemia-related adverse events in these patients was 0.1% during 9 months of follow-up. These improvements in glycemic control were sustained for as long as 32 months in an extension study.^{46,47}

As β -cell function declines over time, supplementing basal insulin with mealtime insulin may become necessary. Evi-

dence suggests that glucose excursions play an important role in vascular damage in patients with diabetes mellitus.^{48,49} Moreover, in addition to regulating glucose levels, insulin regulates triglyceride metabolism, and inadequate production of endogenous insulin in patients with

T2DM is associated with hypertriglyceridemia,⁵⁰ which is an independent risk factor for atherosclerosis.⁵¹

Use of RHI at mealtime is limited by the fact that it must be administered subcutaneously at least 30 minutes before meals because of its slow onset of action (30-60 minutes). In addition, RHI has a relatively long duration of action (8-10 hours), resulting in increased risk of postprandial hypoglycemia. The busy schedules of some patients may be restricted by the need for such a long lead-time between insulin administration and eating.

The use of rapid-acting insulin analogs at mealtime provides several advantages over RHI, such as rapid onset of action (≤ 15 minutes), shorter duration of action (4-6 hours), and more predictable insulin action profiles.^{30,35} Because prandial insulin analogs have a more rapid onset and shorter duration of action than RHI, they can be administered as follows at mealtime: 5 to 10 minutes before a meal (insulin aspart), between 15 minutes before and 20 minutes after starting a meal (insulin glulisine), and within 15 minutes or immediately after a meal (insulin lispro).^{35,52} The increased mealtime flexibility afforded by the use of rapid-acting bolus insulins may give patients greater control of their lives.

Minimizing Insulin-Related Adverse Effects

Patients who express concern about insulin-related hypoglycemic episodes should be informed that the risk for serious hypoglycemia (ie, episodes requiring treatment assistance from another individual) is low in cases of T2DM. Based on data from clinical trials designed to manage hyperglycemia aggressively, the estimated risk for a serious hypoglycemic episode in a patient with T2DM is between 1 and 3 in 100 years.^{36,39,40} Physicians may find it useful to explain to patients that although the risk of serious hypoglycemia is low

Agent	Time of Action, h*		
	Onset	Peak	Duration
■ Insulin			
□ Short-acting			
– RHI	30-60 min	2-3	8-10
□ Intermediate-acting			
– NPH	2-4	4-10	12-18
■ Insulin Analog			
□ Long-acting			
– Detemir	0.8-2	peakless	≤24
– Glargine	2-4	peakless	24
□ Rapid-acting, mealtime bolus			
– Aspart	5-15 min	30-90 min	4-6
– Glulisine	15 min	30-90 min	5.3
– Lispro	5-15 min	30-90 min	4-6
■ Premixed			
□ NPH/RHI 70/30	30 min	1.5-2	≤24
□ NPH/RHI 50/50	30 min	1.5-2	≤24
□ Biphasic insulin aspart 70/30	5-15 min	1-4	≤24
□ Insulin lispro protamine/insulin lispro 75/25	15-30 min	≤2	~22
□ Insulin lispro protamine/insulin lispro 50/50	15-30 min	30-90 min	~22

Figure 2. Time action profiles of insulins and insulin analogs. *Units are in hours unless otherwise indicated. **Abbreviations:** NPH, neutral protamine Hagedorn; RHI, regular human insulin. Sources: Hirsch IB. *N Engl J Med.* 2005;352(2):174-183.³⁰ Heise T, et al. *Diabetes Obes Metab.* 2007;9(5):648-659.³² Plank J, et al. *Diabetes Care.* 2005;28(5):1107-1112.³³ Levy P. *MedGenMed-scape.* 2007;9(2):12.³⁴ NovoLog mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection) [package insert]. Princeton, NJ: Novo Nordisk Inc; October 2007.⁵⁹

for patients with type 1 diabetes mellitus, that risk is more than 10 times higher than the corresponding risk for patients with T2DM.⁵³ Providing patients with information on managing mild episodes of hypoglycemia is important and can be reassuring.

Patients should also be informed that the risk of weight gain can be minimized by using newer insulin analogs instead of human insulin regimens.^{30,31} In a clinical study of insulin therapy in patients with T2DM, those patients receiving the insulin analog detemir gained, on average, 1.0 kg, compared to 1.8 kg among patients receiving NPH ($P=.017$), over 26 weeks of therapy.⁵⁴ In a subgroup analysis of insulin-naïve patients with T2DM, those who were prescribed insulin detemir had no statistically significant weight gain during 14.4 weeks of follow-up, with a mean change in body weight of -0.7 kg ($P<.001$).⁴⁴ Moreover, a statistically significant association ($P<.001$) between greater weight reduction and greater baseline body mass index was noted in this analysis.⁴⁴

Patient-Driven Titration Algorithms for Initiating Basal Insulin Therapy

Bridging antidiabetes treatment from oral therapy to insulin therapy by adding basal insulin is a strategy that has been embraced globally because of its simplicity. The premise underlying basal insulin therapy is that at the time insulin therapy is initiated, mealtime insulin secretion by the pancreas is still adequate, or it can be enhanced by a secretagogue.

When starting basal insulin therapy, continued use of oral agents should be evaluated. Basal insulin should be initiated at a dose of 0.1 to 0.2 units per kilogram of body weight.⁵⁵ Most physicians prescribe a starting dose for basal insulin of 10 units, to be taken by the patient every night at 10:00 PM. Once the dose of basal insulin has been established, the patient's FPG levels should be monitored to evaluate the treatment's effectiveness. The target FPG level set by the ADA is between 80 and 110 mg/dL.² Patients should be encouraged to check their FPG levels

at the same time each morning to standardize the monitoring process.

Several titration algorithms are available to guide dosing in basal insulin therapy. The safety and efficacy of a patient-driven titration algorithm was evaluated in the PREDICTIVE 303 study,⁸ a 26-week observational study of the "real-world" use of insulin detemir. A total of 5604 patients with T2DM were assigned to a group using the patient-driven 303 algorithm or to a group using local standards of care. In the 303 algorithm group, patients were advised to calculate the average of their FPG levels over 3 consecutive days (Figure 3).⁸ If a patient's average 3-day FPG level was greater than 110 mg/dL, 3 units of basal insulin were added to the daily dose. If a patient's average 3-day FPG level was between 80 and 110 mg/dL, the insulin dose remained the same. If a patient's average 3-day FPG level was less than 80 mg/dL, 3 units were subtracted from the daily basal insulin dose. In the standard-of-care group, physicians adjusted doses of insulin detemir according to local standards of care.⁸

Compared with patients in the standard-of-care group, patients in the 303 algorithm group achieved significantly greater improvements in HbA_{1c} levels, ($P=.016$) without weight gain.⁸ The overall incidence of hypoglycemia in the 303 algorithm group decreased from 9.05 events per patient-year at baseline to 6.44 events per patient-year at study end ($P=.0039$), while the overall incidence of hypoglycemia in the standard-of-care group decreased from 9.53 events per

Fasting Plasma Glucose, mean, mg/dL (mmol/L)	Dosing
<80 (<4.4)	Reduce by 3 units
80-110 (4.4-6.1)	No change
>110 (>6.1)	Increase by 3 units

Figure 3. Patient-driven self-titration algorithm used in the PREDICTIVE 303 study⁸ (Meneghini L, et al. Diabetes Obes Metab. 2007;9[6]:902-913) for basal insulin analog (insulin detemir) dosing, based on the mean of three fasting plasma glucose levels self-measured for 3 consecutive days.

patient-year at baseline to 4.95 events per patient-year at study end ($P<.001$).⁸

To assess the utility of self-managed insulin titration in patients with no experience using insulin, a post hoc analysis in the PREDICTIVE 303 study compared results of using the 303 algorithm with results of using the standard-of-care approach in 1641 participants initiating insulin detemir.^{8,9} Reductions in HbA_{1c} levels were similar in the two groups at the end of 26 weeks, with a 1.1% decrease in the 303 algorithm group and a 1.0% decrease in the standard-of-care group.⁹ Significantly greater reductions in FPG levels were observed in the 303 algorithm group compared with the standard-of-care group (between-group difference, -19.9 mg/dL; $P=.001$), though both groups achieved statistically significant reductions from baseline.⁹

Rates of overall and daytime hypoglycemic episodes were similar in the two groups in the post hoc analysis of the PREDICTIVE 303 study,⁹ though the incidence of nocturnal hypoglycemia was significantly higher in the self-titration group than in the group receiving standard-of-care treatment (1.02 vs 0.65, respectively; $P=.0323$). The incidence of major hypoglycemic events was low and did not differ between the 303 algorithm group and the standard-of-care group (0.08 events/patient-year vs 0.03 events/patient-year, respectively; $P=.273$).⁹

These data suggest that empowering patients with a self-titration algorithm, such as the 303 algorithm, is safe and effective for initiating insulin therapy and achieving and maintaining intensive glycemic control.^{8,9}

These results are supported by findings from A Trial Comparing Lantus Algorithms to Achieve Normal Blood Glucose Targets in Subjects With Uncontrolled Blood Sugar (AT.LANTUS)^{10,11} and the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study.^{10,11} Each of these trials compared outcomes in patients with T2DM who initiated insulin glargine using either a patient-driven titration procedure or a clinic-directed algorithm. In both studies, good glycemic control with a low incidence of hypoglycemia (<1%) were achieved with both the patient-driven and clinic-directed algorithms.^{10,11}

In the AT.LANTUS trial,¹⁰ patients who were randomized to the patient-driven titration algorithm experienced a greater reduction in HbA_{1c} than patients randomized to the clinic-directed titration algorithm (-1.22% vs -1.08%, respectively; $P<.001$), with no statistically significant between-group differences in incidence of severe hypoglycemia.⁵⁶ Similar results were observed in a subgroup analysis of patients suboptimally controlled on one or more oral agents.¹⁰

The efficacy and tolerability of two patient-driven treat-to-target algorithms for once-daily therapy with insulin detemir have been evaluated in a recent trial.⁵⁷ In one algorithm, the FPG titration target was 80 to 110 mg/dL, and in the second algorithm, the FPG titration target was 70 to 90 mg/dL. Although both algorithms resulted in substantial improvement in glycemic control, patients assigned to the 70-to-90-mg target experienced greater reductions in HbA_{1c} than patients assigned to the 80-to-110-mg target (-1.2% vs -0.9%, respectively; $P=.0019$), with comparable rates of hypoglycemia in both groups.

Initiating Mealtime Insulin Therapy

Regardless of the titration scheme used, basal insulin doses must be titrated to reduce FPG levels to between 80 and 110 mg/dL. Therefore, when the administration of basal insulin fails to control FPG levels after a reasonable titration period, β -cell deterioration has likely occurred to such an extent that more intensive therapy is needed.

Decisions regarding when to transition from basal insulin therapy to a more intensive insulin regimen should be made on a case-by-case basis. However, a few simple calculations of daily insulin requirements can help physicians determine the timing of this step. Although the estimated total daily insulin requirement on a unit-per-kilogram basis varies, clinical experience suggests that the total insulin requirement typically ranges from 0.5 units to 2.0 units per kilogram per 24 hours. Because approximately 50% of a patient's total daily insulin requirement is composed of basal insulin and 50% of bolus or mealtime insulin, if a patient's daily dose of basal insulin is greater than 50% of the estimated total daily insulin dose—and the patient has not achieved FPG goals—intensifying therapy by adding prandial insulin should be considered.

Choosing an Initial Insulin Regimen

Patients with T2DM may be concerned about needing multiple daily injections. Despite the fact that relatively high insulin doses are typically required to overcome insulin resistance in patients with T2DM, once-daily dosing with longer acting insulin analogs are adequate in many patients.^{9,40} During the course of the PREDICTIVE study,⁴⁴ patients with T2DM who had not previously used insulin achieved statistically significant improvements in mean HbA_{1c} values, FPG, and within-patient fasting glucose variability, compared with baseline ($P<.001$ for all three parameters). In this analysis, 82% of

Variable	Basal Favored	Premixed Favored
HbA _{1c} %	≤8.5	>8.5
FPG vs PPG	FPG>PPG	PPG>FPG
Usual administration frequency	QD	BID
Weight gain	+	++
Hypoglycemia	+	++
Lifestyle flexibility	++	+

Figure 4. Comparison of basal insulin vs premixed insulin options for insulin-naïve patients with type 2 diabetes mellitus. Reprinted with permission from Meneghini L, Sheikh A. Update on the use of detemir insulin in the management of type 2 diabetes. *US Endocr Dis.* 2008;4:38-42.⁵⁸ **Abbreviations:** BID, twice daily; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; PPG, postprandial plasma glucose; QD, daily; +, favored; ++, more strongly favored.

patients were able to achieve those improvements with once-daily insulin detemir.⁴⁴ Among individuals initiating insulin therapy using the patient-driven 303 algorithm, 95% used once-daily dosing at the end of the 26-week study.⁹

When limiting the number of daily injections may be beneficial to the patient's ability to manage T2DM, the use of either basal insulin or premixed insulin may be considered. Several objective criteria can help clinicians decide between basal insulin or premixed insulin regimens (Figure 4).⁵⁸ For individuals whose HbA_{1c} values are greater than 8.5% and for those whose postprandial glucose levels are elevated, initiation of therapy with premixed insulin analogs should be considered (Figure 2).^{30,32-35,59} Premixed insulin analogs can simplify therapy for patients who require postprandial control in addition to basal insulin. These premixed formulations eliminate the need to prepare multiple insulins and reduce the number of daily injections.⁶⁰

Compared with the addition of basal insulin to oral antidiabetes therapy in insulin-naïve patients, the addition of premixed analog insulin to the therapy regimen has been found to result in lower mean HbA_{1c} values and in a greater probability of achieving target HbA_{1c} values of less than 7%.^{61,62} However, patients receiving premixed insulin analog therapy also gained more weight and had a greater risk of minor hypoglycemic episodes than patients receiving basal insulin.^{61,62}

Because premixed insulin analog formulations use insulin analogs that have a shorter duration of action than does RHI, dosing of premixed insulin analogs is more flexible than dosing of premixed human insulin. A recent systematic review of eight studies found that, compared with premixed human insulin formulations, premixed insulin analogs resulted in a greater decrease from baseline in postprandial glucose (mean difference between groups, -19.2 mg/dL; 95% confidence

interval [CI], -25.9 to -12.5).⁶³ Both types of treatment achieved similar decreases from baseline in HbA_{1c} values (mean difference in decrease, -0.05%; 95% CI, -0.14% to 0.04%).⁶³ Rates of major and minor hypoglycemic episodes were also similar between groups.⁶³

Basal-bolus insulin regimens provide another option with some benefits, but some patients may prefer premixed insulins because premixed insulins require fewer injections per day. However, patients should be informed of potential trade-offs in achieving glycemic control with premixed formulations. A randomized, open-label trial (N=374)³⁶ compared the safety and efficacy of a regimen of premixed insulin lispro protamine/insulin lispro with a regimen of glargine as basal insulin and lispro as prandial bolus insulin. In this study,³⁶ a significantly greater percentage of patients using the basal-bolus insulin regimen achieved target HbA_{1c} values of less than 7%, compared with patients using the premixed insulin regimen (69% vs 54%, respectively; *P*=.009). Rates of hypoglycemic episodes were similar in the two treatment groups.³⁶

Although these results require confirmation, they suggest that patients and clinicians need to consider evidence that increasing the number of injections per day with basal-bolus insulin analogs is likely to improve glycemic control. Both basal-bolus and premixed insulin regimens have similar flexibility of dosing, with no apparent difference in risk of hypoglycemia.³⁶ Thus, rather than choosing a premixed insulin regimen over basal-bolus insulin on the basis of a patient's injection-related anxiety, efforts should be made to help the patient explore ways to reduce those anxieties.

Enhancing the Convenience and Safety of Insulin Therapy

Anxiety about injections is one of the most commonly cited reasons for the reluctance of patients to use insulin therapy. Currently, pharmaceutical companies that market insulins also market one or more pen devices that are designed to deliver their products conveniently, accurately, and safely. Educating patients about the advantages of these pen devices may help them feel more comfortable with insulin therapy in general.

From the patient's perspective, clinical studies comparing insulin pens to vial- and syringe-based insulin delivery systems have demonstrated that insulin pens are preferred overwhelmingly and improve patient adherence to treatment regimens.⁶⁴ Insulin pens also improve patient confidence about their ability to achieve glycemic control,⁶⁵ provide greater flexibility in lifestyle and quality of life,^{64,66,67} and are easier to use and read.⁶⁸ One study involving hospitalized patients who were randomized to receive insulin administered via either pens or conventional vials and syringes showed that significantly more patients in the pen group self-injected at least one dose of insulin during hospitalization, compared with the vial-and-syringe group (77% vs 13%, respectively;

$P=.001$).⁶⁹ In addition, more patients in the pen group than the vial-and-syringe group expressed a willingness to continue using insulin at home with their assigned method (74% vs 45%, respectively; $P<.05$) and to recommend their method of insulin administration to other patients with diabetes mellitus (94% vs 73%, respectively; $P<.05$).⁶⁹

Insulin pens also may be associated with lower rates of hypoglycemia, according to data from recent observational studies.^{70,71} In addition, these devices have been shown to enhance patient adherence to prescribed insulin regimens.⁷² In a survey of 600 patients with T2DM, the probability that an individual was a pen user was increased among those who believed that pens could make self-care easier, compared with those who did not have this belief (OR, 20.2; $P<.001$).⁷³ Probability of pen use was also increased among patients whose physicians had discussed pens as an option, compared with those whose physicians did not discuss pen use (OR, 14.1; $P<.001$).⁷³ However, the OR for pen use was 135.6 ($P<.001$) for patients whose doctors recommended the pen, suggesting that a physician's recommendation substantially increases pen use.

Cost was the most commonly reported reason given by patients in the survey for not using an insulin pen.⁷³ Thus, by discussing the costs vs the benefits of insulin pen delivery systems, physicians can empower patients to make educated decisions about their treatment.

Conclusion

It is unfortunate that insulin therapy—the most effective and most established glucose-lowering agent for patients with diabetes mellitus—is often avoided or delayed in clinical practice. Many patients have concerns, including some misconceptions, about insulin therapy. Physicians need to understand their patients' concerns and refer them to resources—such as CDEs and DSME programs—that can help patients overcome barriers to effective glycemic control.

Evidence indicates that empowering patients to take greater control of their diabetes mellitus through education and patient-oriented insulin titration regimens may improve glycemic control and reduce the risk for complications. Key components of educational initiatives designed to empower patients include instruction about the need for insulin, the importance of insulin in glycemic control, the benefits of newer and more physiologic insulin analogs, and the role of patient-friendly insulin regimens and delivery systems.

Using patient-driven insulin titration regimens may also help patients with diabetes mellitus become more involved in their own treatment and achieve greater glycemic control, compared with the use of physician-directed dose adjustments.

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