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Practical Strategies to Improve Treatment of Type 2 Diabetes

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This white paper is authored by our faculty member, Evelyne Fleury Milfort, and published in the Journal of American Association of Nurse Practitioners (JAANP), June 2008.

It addresses practical strategies to improve treatment of type 2 diabetes. The purpose of this review is to document the need for, barriers to, and available treatment options for patients with type 2 diabetes, with a focus on modern insulins and delivery systems.

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PRACTICE

Practical strategies to improve treatment of type 2 diabetes

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Keywords

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Abstract

Purpose: The purpose of this review was to document the need for, barriers to, and available treatment options for patients with type 2 diabetes, with a focus on modern insulins and delivery systems.

Data sources: Extensive review of the scientific literature was carried out, concentrating on data supporting the need for tight glycemic control, and efficacy and safety data on oral antidiabetes agents, insulins (particularly insulin analog therapies), incretins, and insulin delivery devices.

Conclusions: Nurse practitioners and other clinicians need to be aware of the urgent need to help patients optimize glycemic control using therapies that can bring blood glucose levels within the target range throughout the day. Choice of therapy must take into account anticipated hemoglobin A_{1c} decrease, tolerability, effect on comorbid conditions, and cost. As diabetes progresses, insulin is the only hypoglycemic agent with unlimited potential to lower blood glucose; earlier initiation of insulin therapy can help many patients achieve glucose targets more rapidly and provide symptomatic relief. Modern insulins and related therapies in conjunction with innovative delivery devices, appropriate counseling, and patient education can help overcome many barriers to insulin therapy.

Implications for practice: The incidence of type 2 diabetes is increasing at an alarming rate. More aggressive treatment, based on the pathophysiology of the disease, is necessary and should include greater attention to control both fasting and postmeal glucose excursions, as well as earlier introduction of insulin therapy that is both effective and acceptable to patients. The educated use of oral antidiabetes agents, modern insulin analogs, incretin agents, and innovative delivery devices can help many patients achieve blood glucose targets in a scientifically logical manner that takes into account a patient's lifestyle needs.

Introduction

It is well known that the number of individuals with type 2 diabetes is increasing rapidly, and disease onset is occurring at progressively earlier ages (Alberti et al., 2004; Wild, Roglic, Green, Sicree, & King, 2004). This situation is a serious challenge, considering the possible burden that diabetes-related complications can impose on the health-care system. As clinicians, if we want to prevent the inevitable consequences of poor glycemic control in this growing population, we must concentrate our efforts

toward treating patients to target, based on our understanding of the pathophysiology of the disease.

Failure to normalize blood glucose in our patients may be partially because of patient factors such as misconceptions about diabetes, myths regarding insulin therapy, and inadequate understanding of the consequences of poor control. We must also recognize that healthcare professionals' comfort level with using the strategies available and concerns over possible hypoglycemia have prevented a more proactive and aggressive approach to achieving target blood sugar. This article discusses how new tools and

treatment regimens, if applied in a timely and appropriate fashion based on the current understanding of the pathophysiology of the disease, can help many more patients achieve optimal levels of glyceemic control.

The typical case

The spectrum of patients with type 2 diabetes presenting to nurse practitioners or physician assistants for help with their diabetes management is quite variable, and thus, case management must be individualized. Nevertheless, for purposes of discussing treatment regimens, let us consider the case of John, a 48-year-old male with type 2 diabetes of 5 years' duration, hypertension, hyperlipidemia, and a body mass index of 32 kg/m². He came to the office with complaints of feeling poorly and pain in his lower extremities. He is on maximum dosage of sulfonylurea + metformin, with a fasting plasma glucose of 284 mg/dL and hemoglobin A_{1c} of 9.6% at his first visit. He had a blood glucose monitor that he was using occasionally, but he lost it 6 months ago.

The need for tight glyceemic control

We all know that diabetes is a serious disease, and the consequences of persistently elevated blood glucose include stroke, retinopathy leading to blindness, kidney disease, erectile dysfunction, neuropathy, peripheral vascular disease, and diabetic foot disease, as well as mortality from cardiovascular causes (Stratton et al., 2000). The good news is that, as shown in Figure 1, efforts toward better control pay off. Numerous studies have demonstrated the importance of blood sugar control in the prevention of these complications (DCCT Research Group, 1993; Shichiri, Kishikawa, Ohkubo, & Wake, 2000;

Stratton et al., 2000). In addition, in the United Kingdom Prospective Diabetes Study (UKPDS), the risk of myocardial infarction, stroke, and heart failure was decreased by 14%, 12%, and 16% per 1% reduction in hemoglobin A_{1c} respectively, and by as much as 43% for peripheral vascular disease (Stratton et al., 2000; Figure 1). Based on these results, professional organizations such as the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have published clinical standards and protocols to guide healthcare professionals in optimizing diabetes management. However, the sad reality is that most individuals with diabetes are not reaching the current population targets proposed by these organizations (<7.0% proposed by the ADA [2006] and ≤6.5% by the AACE [Lebovitz et al., 2006]), which research suggests are too conservative. Even apparently small improvements in glyceemic control can have great clinical impact: each 0.5% reduction in hemoglobin A_{1c} is associated with an 11.5% decrease in risk of complications of diabetes. The opposite is also dramatic. In one epidemiologic study, any increase in hemoglobin A_{1c} above 5% was associated with increased risk for cardiovascular disease and all-cause mortality (Khaw et al., 2004). Our goal should be to normalize, not just lower, blood sugar. In fact, the most recent ADA clinical practice recommendations advise that individuals strive for hemoglobin A_{1c} < 6.0%, provided hypoglycemia can be avoided (ADA).

However, close attention to hemoglobin A_{1c} alone is insufficient to ensure optimal glyceemic control. Hemoglobin A_{1c} represents average blood glucose during the previous 3 months (approximately) but cannot indicate the quality of control on a daily basis. Therefore, it is possible for a patient to have hemoglobin A_{1c} approaching targets, yet still have intermittent but frequent postprandial glucose

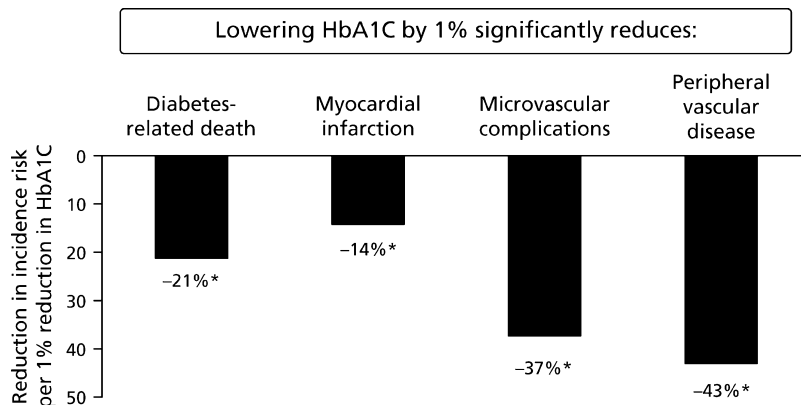


Figure 1 Improvements in glyceemic control significantly reduced complications of type 2 diabetes (UKPDS).

Note. Data from Stratton et al. (2000).

*p < .0001.

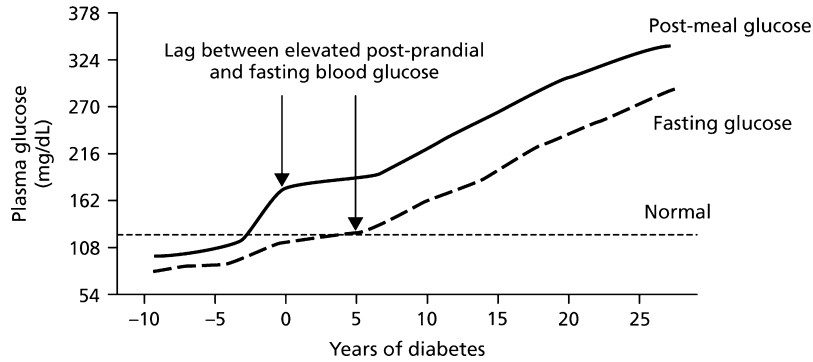


Figure 2 Postmeal glucose increases years before fasting blood glucose in patients with type 2 diabetes. Note. © 2003 Kendall and Bergenstal.

excursions (i.e., after meals) that expose them to all the unwanted effects of hyperglycemia. As shown in Figure 2, postmeal glucose is likely to be raised for several years before there are detectable elevations in fasting blood glucose. In a study of more than 1100 patients newly diagnosed with type 2 diabetes, poor mealtime blood glucose (measured 1 h after a patient’s normal breakfast), but not fasting blood glucose, was a significant risk factor for mortality during the 11-year follow-up ($p < .05$). These findings take on additional importance when considering that most people spend about 50% of the time in the postmeal state (Monnier, 2000). Furthermore, the relative contribution of mealtime glucose to overall hemoglobin A_{1c} levels increases as overall glycemic control improves (Monnier, Lapinski, & Colette, 2003; Figure 3). In the case of our typical patient presented here (hemoglobin A_{1c}: 8.0%–9.0%), mealtime glucose contributes about half of total hemoglobin A_{1c}.

Treatment options

Several options are possible for treating John, who has not reached targets on dual oral therapy. First, we will need to check how well John is applying therapeutic lifestyle

changes (TLC) and work with him and his family to help enhance their knowledge and skills in this area. However, we have to be mindful that, although TLC may decrease hemoglobin A_{1c} by 1%–2%, follow-through tends to fail after 1 year. Consequently, the latest consensus paper suggests starting newly diagnosed patients on TLC and metformin concurrently (Nathan et al., 2006). Metformin may decrease hemoglobin A_{1c} by up to 1.5%, has a positive effect on lipids, is weight neutral, or may lead to mild weight loss in some patients. Although it can have gastrointestinal (GI) side effects, metformin is generally well tolerated by most patients without severe complications when clinical indications are followed and is inexpensive.

Now, let us look at John’s pharmaceutical management. According to the recent consensus algorithm for the management of type 2 diabetes, decision making should be guided by several factors: the expected hemoglobin A_{1c} lowering, tolerability, effect on comorbidity, and cost (Nathan et al., 2006). For John, adding a thiazolidinedione (TZD) to existing metformin and sulfonylurea therapy to create a triple-therapy regimen would not be the most efficient strategy. Based on the expected hemoglobin A_{1c} decrease of 0.5%–1.4%, this is most likely to be effective in

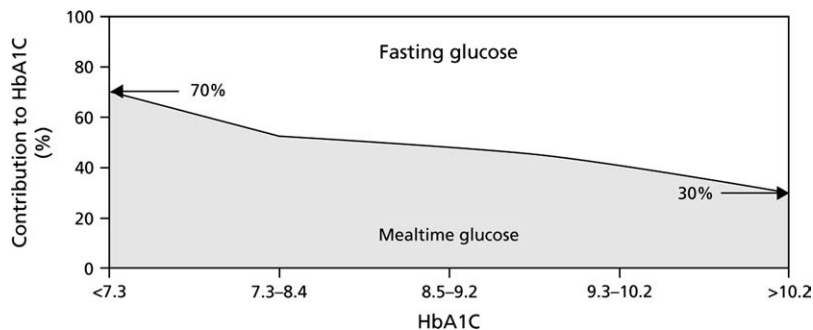


Figure 3 Mealtime glucose makes its greatest contribution to hemoglobin A_{1c} in patients who have the best overall control. Note. Data from Monnier et al. (2003).

those patients whose hemoglobin A_{1c} is no more than about 8.0% (Riddle, 2005). It should be noted that TZDs have the advantage of improving blood lipids (Nathan et al., 2006). Undesirable consequences of TZD treatment include weight gain and fluid retention. These agents are also relatively costly, and in addition, liver function needs to be monitored. At this time, in the treatment of patients like John, adding a glinide would be inappropriate as this treatment strategy would not yield more insulin secretory capacity. An alpha-glucosidase inhibitor would also be unwise as it would have little or no effect on his fasting blood sugar, and this class of drug only has a modest effect on the hemoglobin A_{1c}.

Addition of an incretin is an increasingly popular option. This class of compounds mimics or enhances actions of natural GI hormones that help regulate metabolism and eating behavior. Exenatide (Byetta; Amylin Pharmaceuticals Inc., San Diego, CA) is a glucagon-like peptide-1 receptor agonist that has been approved for patients with type 2 diabetes who are unable to achieve glycemic control using other oral antidiabetic drugs (OADs; metformin ± sulfonylureas ± TZD). For John, this could have the possible added benefit of weight loss. Exenatide works by slowing gastric emptying and decreasing the sensation of hunger. It also enhances existing nutrient-stimulated insulin secretion and suppresses glucagon levels, leading to reduced hepatic glucose production. In a 30-week, randomized, placebo-controlled trial in 733 people with type 2 diabetes who were unable to achieve glycemic control with metformin + sulfonylurea therapy, 34% of subjects taking exenatide 10 µg daily (plus OADs) and 27% of those taking exenatide 5 µg daily (plus OADs) reached hemoglobin A_{1c} ≤ 7.0%, compared with only 9.0% of those continuing on metformin + sulfonylureas ($p < .0001$; Kendall et al., 2005). Each group on exenatide also lost a mean of 1.6 ± 0.2 kg from baseline. Of course, the efficacy of such a regimen depends on the level of baseline glycemic control and the extent of endogenous insulin secretion. The recent consensus statement indicates that the expected decrease in hemoglobin A_{1c} with exenatide would be 0.5%–1.0% (Nathan et al., 2006). GI side effects are also the main potential problem, and like insulin, exenatide must be given by injection.

Sitagliptin phosphate, a dipeptidyl peptidase-4 (DPP-4) inhibitor recently approved by the Food and Drug Administration as monotherapy and as add-on therapy to either metformin or TZDs, is not approved with sulfonylureas, as the risk of hypoglycemia is unknown. Like exenatide, but through a different mechanism, sitagliptin phosphate enhances the incretin system to help regulate glucose by affecting the beta- and alpha-cells in the pancreas. Through DPP-4 inhibition, sitagliptin phosphate works only when blood sugar is elevated to address diminished

insulin because of beta-cell dysfunction and uncontrolled production of glucose by the liver because of alpha- and beta-cell dysfunction. Its effect on weight is neutral. The sitagliptin phosphate effect in hemoglobin A_{1c} lowering appears to be related to the degree of hemoglobin A_{1c} elevation at baseline. In a pooled analysis of two monotherapy studies, a prespecified subgroup analysis showed that when patients were grouped by baseline hemoglobin A_{1c} into those with mildly elevated hemoglobin A_{1c} levels (<8%, $n = 411$), those with moderately elevated hemoglobin A_{1c} levels (>8% to <9%, $n = 239$), and those with the highest elevated hemoglobin A_{1c} levels (>9%, $n = 119$), mean differences in hemoglobin A_{1c} from placebo after 18 weeks were -0.6% , -0.7% , and -1.4% , respectively ($p < .001$; *Sitagliptin prescribing information*). Stuffy or runny nose and sore throat, upper respiratory infection, and headache are the most common side effects reported with sitagliptin phosphate. This medication would not be a good choice for John because the expected hemoglobin A_{1c} decrease would not be sufficient to reach target, especially if his sulfonylureas had to be removed. Like TZDs, this drug has only a modest hemoglobin A_{1c}-lowering effect and is costly.

Another, more appropriate, option is to initiate insulin therapy. Unfortunately, many patients with type 2 diabetes, as well as their healthcare providers, may feel that insulin is a treatment to be avoided (Peyrot et al., 2005). This attitude fails to recognize that type 2 diabetes is a disease with progressive decline in beta-cell secretion that, for most patients, will eventually require insulin supplementation and later replacement (UKPDS, 1998; Wright et al., 2002).

Planning for insulin therapy

Despite the availability of five different classes of OADs, insulin remains the only medication that can theoretically bring any patient to target if appropriate dosage is used, limited only by potential for hypoglycemia and with the advantage of a positive effect on lipids. Unfortunately, insulin remains underused in type 2 diabetes, and when it is used, it is often delayed and/or not titrated sufficiently (Riddle, Rosenstock, Gerich, & Insulin Glargine 4002 Study Investigators, 2003). Failure to realize the potential of insulin therapy for achieving tight control can be attributed to a variety of barriers, all of which can potentially be overcome (Table 1).

The most common patient barriers are fear of beginning an injection regimen, including the implications of insulin therapy concerning progression; time; cost; and complications. Many clinicians tend to use scare tactics as a way to bring patients to follow treatment recommendations. In my own experience, much of the fear of insulin can be

Table 1 Overcoming barriers to insulin therapy in type 2 diabetes

Barrier	Response or strategy for overcoming barrier
Physical barriers	<ul style="list-style-type: none"> ● Provide assistance with injection ● Select a regimen minimizing the number of injections ● Select a less complex regimen ● Use a modern delivery device instead of syringe
Fear of needles or injections	<ul style="list-style-type: none"> ● Reassure that many patients have this fear ● Show the patient an injection device—patients often think that they will need to use long needles ● Highlight that the injection is into fat, not a vein ● Get first injection out of the way as soon as possible ● Discuss use of specific devices to address this fear ● If patient has severe needle phobia, consider use of injection aids or referral to secondary psychological care
Fear of injecting in public	<ul style="list-style-type: none"> ● Suggest regimen involving fewer injections, decreasing likelihood of need to inject in public ● Suggest coping strategies ● Discuss discretion of using a modern injection device
Are they becoming more ill/feelings of failure	<ul style="list-style-type: none"> ● Discuss as part of initial education and reinforce over time that type 2 diabetes is a progressive disease; hence, treatment has to change as the disease progresses ● This is an expected part of the disease process: insulin is a hormone that will have to be supplemented and later replaced ● Use of insulin will help achieve control and minimize the risk of complications
Concerns over hypoglycemia	<ul style="list-style-type: none"> ● Reassure the patient that hypoglycemia is relatively rare ● Educate the patient on how to prevent and recognize symptoms ● Make sure the patient and partner/family (if applicable) know how to deal with it
Cost	<ul style="list-style-type: none"> ● Insulin therapy may be less expensive than triple oral therapy
Concerns over weight gain	<ul style="list-style-type: none"> ● Encourage healthy food intake and moderate exercise ● Explain that initial weight gain may be associated with improved control but does not necessarily continue indefinitely ● Combine insulin with metformin ● Consider using an insulin formulation less associated with weight gain^a

Note. Adapted from MERIT educational website (UK).

^aFrom Haak et al. (2005) and Raslova et al. (2006).

mitigated if patients are introduced early in their diabetes education to the likely need for insulin at some stage. By discussing with them the progressive nature of type 2 diabetes, patients can come to regard insulin supplementation and eventual replacement as a normal and expected development. I usually tell them that insulin is a hormone that will eventually need to be replaced. This is also the time to emphasize the importance of blood glucose control and the role of lifestyle modifications in postponing this process.

For patients like John, we must keep in mind that optimal control does not need to occur all at once; as long as the desired target is kept in mind, intensification can take place gradually. The important point is to keep patients progressing at a rate that is achievable, comfortable, and safe for them. Potential complications of insulin therapy must be thoroughly explained and kept in perspective. For example, it is important to communicate that there may be some initial weight gain, or some swelling from osmotic shift, and that the blurred vision that can occur when insulin is initiated—especially after severe hyperglycemia—is not the same as the retinopathy that arises as a long-term complication of poor control. It may be important for some patients that insulin therapy may actually be less costly than triple oral therapy (Schwartz et al., 2003).

The result of these barriers and beliefs is that many people with type 2 diabetes, including those using insulin, continue to live with suboptimal glycemic control. Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) survey indicate that only half (49.8%) of the U.S. adults with diabetes had hemoglobin A_{1c} < 7% and nearly one third (29.7%) had values ≥ 8.0% (Resnick, Foster, Bardsley, & Ratner, 2006). Only about 27% of the sample reported using insulin. Clinicians must remember that in the treatment of type 2 diabetes compared to type 1 diabetes, larger dosages of insulin may be required to help overcome insulin resistance.

New insulin analogs

Ideally, insulin therapy should reproduce normal insulin secretion during fasting and after meals. Unfortunately, conventional insulins and traditional therapy regimens fail to accomplish this. The result has been either poor control or increased risk of hypoglycemia, neither of which is desirable. Although neutral protamine Hagedorn (NPH) insulin may still have a place in the management of certain patients who do not want to take too many injections and need lunchtime coverage, insulin analogs represent an important advance in technology as they overcome, at least partially, some of the major limitations of conventional insulins and better approximate physiological

insulin secretion. Insulin analogs are available in basal, rapid-acting, and premixed formulations (Table 2). The rapid-acting insulin analogs all have a more rapid onset of action and reach peak concentration much faster than regular human insulin (Becker, Frick, Burger, Potgieter, & Scholtz, 2005; Homko, Deluzio, Jimenez, Kolaczynski, & Boden, 2003). The main advantage conferred by this change is that patients can inject at the start of a meal or 10–20 min afterward, depending on the insulin, instead of the 30 min prior to meals recommended for regular human insulin or premixed human insulin. This feature allows more flexibility in meals and also lets patients better match insulin dose to the actual carbohydrate intake. Postmeal dosing is also possible for the premixed analog biphasic insulin aspart 30 (BIAsp 30, –15 to +15 min; *NovoMix product insert*); lispro 75/25 is only approved for premeal dosing (–15 to 0 min; *Lispro 75/25 product insert*).

The two basal analog insulins have a longer duration of action and a relatively flat time action profile without a pronounced peak and less variability in their absorption compared to NPH (Haak, Tiengo, Draeger, Suntum, & Waldhausl, 2005; Lepore et al., 2000; Raslova et al., 2004; Riddle et al., 2003). This feature should make them more predictable in their glucose-lowering action, compared to NPH, and likely contributes to the lower incidence of hypoglycemia in type 2 diabetes (Hermansen et al., 2006; Raslova et al., 2004; Riddle et al.; Rosenstock et al., 2001; Yki-Jarvinen, Dressler, Ziemer, & HOE 901/300s Study Group, 2000). In one recently published treat-to-target study, the incidence of all hypoglycemia in subjects treated with insulin detemir was reduced by 47% and nocturnal hypoglycemia by 55%, compared with NPH (Hermansen et al., 2006). In another treat-to-target trial comparing insulin glargine to NPH, hypoglycemia was reduced by 21%, 29%, and 41%, for all symptomatic

events, confirmed events ≤ 72 mg/dL, and confirmed events ≤ 56 mg/dL, respectively (Riddle et al.). Clinical studies indicate that of the two basal analogs, insulin detemir appears to have the least within-patient variability in insulin action (Heise et al., 2004; Klein et al., 2007). Another feature to be aware of, which may be of particular importance for overweight patients, is that insulin detemir has consistently been associated with lesser weight gain than NPH in type 2 diabetic patients (Haak et al., 2005; Hermansen et al., 2006; Meneghini, Rosenberg, Koenen, Merilainen, & Lüddecke, 2007; Raslova et al., 2004).

Choosing an insulin regimen

There are many different treatment regimens available for type 2 diabetes, but those involving insulin can be divided into three general types:

1. Basal insulin + OADs
2. Split-mixed or premixed insulin once or twice daily \pm OADs
3. Basal–bolus regimen.

Each regimen has advantages and disadvantages (Table 3), and the selection of a regimen needs to be tailored to the needs and abilities of individual patients, who should be involved in the process at every stage. Supplementation with basal insulin regimens, usually used in conjunction with OADs such as metformin, sulfonylureas, or TZDs, offer the advantage of requiring only one daily injection usually given at bedtime, and slowly titrating the dose upward, based on fasting blood sugar. This is a popular starting regimen because of its simplicity. This regimen allows patients like John to improve glycemic control while becoming used to managing insulin self-injection and the blood glucose monitoring that should accompany it. One drawback of basal insulin regimens is

Table 2 Commercially available insulin analogs and their advantages over conventional human insulin formulations

Type	Generic name	Brand (manufacturer)	Improvement over conventional insulin
Rapid acting	Insulin aspart	NovoLog (Novo Nordisk)	Higher peak concentration, faster time to onset, and can administer closer to meals.
	Insulin lispro	Humalog (Eli Lilly)	
	Insulin glulisine	Apidra (Sanofi-Aventis)	
Basal	Insulin detemir	Levemir (Novo Nordisk)	More predictable glucose-lowering effect, flatter profile without a pronounced peak, prolonged action, and less hypoglycemia. Each can be used once daily.
	Insulin glargine	Lantus (Sanofi-Aventis)	
Premixed	BIAsp 30 ^a	NovoLog Mix 70/30 (Novo Nordisk)	Higher peak concentration, faster time to onset, and can administer closer to meals.
	Biphasic insulin lispro mix 25 (lispro 75/25) ^b	Humalog MixTM75/25 (Eli Lilly)	
	Biphasic insulin lispro mix 50 (lispro 50/50) ^c	Humalog Mix 50/50 (Eli Lilly)	

^aContains 30% insulin aspart and 70% protaminated insulin aspart.

^bContains 25% insulin lispro and 75% protaminated insulin lispro.

^cContains 50% insulin lispro and 50% protaminated insulin lispro.

Table 3 Advantages and disadvantages of three common insulin regimens

Insulin regimen	Advantages	Disadvantages
Basal insulin with OADs	<ul style="list-style-type: none"> ● A simple starting regimen for insulin-naïve patients, requires only one injection per day ● Particularly useful when patient's blood glucose is high overnight and in the morning ● Convenient for patients who require a third party to administer their insulin ● With stable control, can test two to three times weekly, but with OADs need daily testing 	<ul style="list-style-type: none"> ● Does not provide insulin specifically for postmeal glucose control and assumes that patient can produce sufficient insulin to cover mealtime requirements ● Dosing during the day is inflexible, so patients need to keep to stricter and more predictable diet ● Temporary and likely to require a change in regimen
Premixed insulin, with or without OADs	<ul style="list-style-type: none"> ● Targets mealtime glucose as well as fasting glucose ● Can be initiated as one injection per day to familiarize patient with injecting ● Second or third daily injections of same insulin in same device can be added if necessary to optimize control ● Can use this regimen long term 	<ul style="list-style-type: none"> ● May not cover lunchtime glucose excursions (if only used once or twice daily) ● Requires regular scheduled meals, consistent carbohydrate intake, and physical activity level ● Does not allow for incremental adjustment of individual components within the premix ● Should test at least twice daily
Basal-bolus multi-injection regimen	<ul style="list-style-type: none"> ● Most physiological insulin replacement regimen (other than insulin pump) ● Opportunity to achieve very tight glycemic control ● Can use this regimen long term ● Improved lifestyle flexibility 	<ul style="list-style-type: none"> ● Requires most skills <ul style="list-style-type: none"> ○ Frequent monitoring of glucose ○ Adjusting dose ○ Four or more daily injections using two different insulins ○ Carbohydrate estimation ○ Problem-solving skills ○ Higher learning curve ○ Skillful clinician

Note. Adapted from the MERIT educational website.

OADs, oral antidiabetic drugs.

that they do not provide mealtime glucose control, so they work best in patients who have sufficient endogenous glucose production remaining to take care of mealtime insulin requirements. Because of the slow progressive decline in insulin secretion, eventually most patients on a basal-only regimen will require mealtime insulin. One option for these patients is to use a once-daily injection of premixed insulin regimen, usually with dinner. The primary advantage of this approach is that patients can stay on the same regimen for a longer period, as both mealtime and fasting glucose are addressed (Malone, Bai, Campaigne, Reviriego, & Augendre-Ferrante, 2005; Malone et al., 2004; Raskin et al., 2005).

As insulin deficiency progresses, patients will require coverage of more than one meal with prandial insulins. In this phase, the secretagogue, such as sulfonylurea, is no longer needed; however, insulin sensitizers such as metformin or TZDs can be continued to decrease insulin resistance. Several insulin replacement regimens can be initiated, such as split-mixed dosing with NPH and rapid-acting insulin. This option can be considered if patients are unwilling or unable to take more than two daily injections and have stable activity levels and consistent intake of carbohydrates. In this regimen, the dosage of rapid-acting insulin can be constant or the patient can be given a dosage

algorithm or guidelines to help adjustment toward glycemic targets. A variant of this option for patients who are unable or unwilling to mix insulin is the use of a twice-daily premixed analog. Several studies using either lispro 75/25 or BIAsp 30 twice daily have demonstrated that more patients can reach target glucose on such a regimen than on a once-daily regimen of insulin glargine. In the INITIATE treat-to-target trial, 66% of patients using BIAsp 30 twice daily with metformin (\pm TZD) reached hemoglobin A_{1c} < 7.0% compared to 40% of those using glargine once daily + metformin (Raskin et al., 2005). By comparison, in the two trials using lispro 75/25 + metformin (other OADs discontinued), the proportion reaching hemoglobin A_{1c} \leq 7.0% was 30% vs. 12% for lispro 75/25 (Malone et al., 2005) and 42% vs. 18% (Malone et al., 2004) for insulin glargine.

The most efficient and physiological way to replace insulin is the basal-bolus regimen, also referred to as multiple daily injections, in which patients take long-acting insulin to cover their basal needs and cover their carbohydrate intake with boluses of rapid-acting insulin. Supplemental dosages are added to cover blood sugars outside target range. This option is good for patients interested in tighter control, in need of flexibility, willing and having the ability to test their blood sugar three to four

times a day, and able to use the results to determine their insulin dosage. It requires more skill on the part of both the patient and the clinician.

For patients who need replacement therapy, who are unwilling or unable to use the above-mentioned basal-bolus regimen, and who have a stable physical activity and carbohydrate intake, one regimen that I have been successfully using for several years is three times daily (TID) premixed insulin. A recent clinical study (1-2-3 Trial) has shown that it is possible to use BIAsp 30 safely once, twice, or up to three times a day to achieve glucose targets (Garber et al., 2006). After 16 weeks of once-daily use, 21% of the patients achieved hemoglobin A_{1c} ≤ 6.5% and 41% reached a hemoglobin A_{1c} < 7%; these proportions increased to 52% and 70% of patients, respectively, when those who moved to twice-daily use were included. A small number of patients increased to TID, bringing the proportions reaching these targets to 65% and 77%. More importantly, using BIAsp 30 TID was not associated with any increased risk of hypoglycemia: the frequency of minor events was 15.4, 22.4, and 12.0 events/patient/year, for once-, twice-, and thrice-daily dosing. In certain circumstances, for example, where the patient likes to snack on carbohydrates but does not like to take additional injections, a TID regimen would be possible using human premixed insulin. However, its extended duration of action would increase the risk of hypoglycemia if a snack is missed.

Patients can be brought to target using either aggressive or conservative titration algorithms with any of these regimens. It should be kept in mind that the treat-to-target regimens derived from clinical trials represent an aggressive approach because of the time constraints of a trial and may need to be modified for use in general practice. Simple and advanced dosing regimens for basal and premixed insulin analogs are presented in Table 4. These should be used only as guides and modified to accommodate the needs, wants, and abilities of individual patients.

Insulin delivery devices

Some of the patient barriers to initiation of insulin therapy have been fear of needles, difficulty managing with the syringe and vial system, and association of syringes with drug addiction. During the past 10 years, a variety of advanced pen-type delivery devices have been developed to make self-injection easier, less painful, more accurate, and more convenient than ever before. Although widely used in Europe, they have been slower to gain acceptance in the United States (Bohannon, 1999). The appearance and many of the features of these new devices may also be helpful in aiding patients who are reluctant to use insulin, the only limitation being insur-

Table 4 Simplified regimen for basal insulin analogs and premixed insulin analogs

Glargine or detemir once daily		BIAsp 30 or lispro 75/25 twice daily ^a	
Blood glucose (mg/dL)	Insulin dose adjustment (U)	Blood glucose (mg/dL) prebreakfast or predinner value ^b	Insulin dose adjustment (U)
>250	+4 to +8	>250	+2 to +4
140–250	+2 to +4	140–250	+1 to +2
70–139	0	70–139	0
<70	–1 to –2	<70	–1 to –2

Note. Simplified regimens drawn from data from International Diabetes Center and Pearson and Powers (2006); Table 3 for basal insulins and Table 4 for premixed insulins.

^aNote that BIAsp 30 can also be used once daily and titrated up to TID administration if needed (Garber et al., 2006).

^bPredinner doses adjusted on the basis of fasting (prebreakfast blood glucose) and prebreakfast doses adjusted on the basis of predinner blood glucose values.

ance coverage. Studies have shown that most patients rate these new devices more highly than vial and syringe in terms of lifestyle flexibility, quality of life, and overall preference (Bohannon; Graff & McClanahan, 1998; Korytkowski, Niskanen, & Asakura, 2005).

A range of devices are available, most of which have a very discreet appearance resembling a pen: for some patients, these devices are less associated with “drugs.” The two basic types are prefilled disposable devices and reusable devices, which require the insertion and changing of a cartridge filled with insulin. It is important to remember that devices are often insulin specific; thus, selection may dictate the choice of insulin, or vice versa. A prefilled disposable device might be best for a patient with a busy lifestyle who needs to keep a pen in the office, car, travel kit, or sports bag, for example. A prefilled device may be a better choice for patients with limited manual dexterity (FlexPen [Novo Nordisk A/S, Bagsvaerd, Denmark], Solo-Star [Sanofi-Aventis, Bridgewater, NJ], and Lilly Prefilled Pen [Eli Lilly, Indianapolis, IN]). Other devices, such as Innolet (Novo Nordisk) are designed to accommodate patients with poor vision. All these devices use small-gauge needles and offer features such as single-unit doses and an audible click for dose confirmation. Two reviews of clinical studies conclude that pens provide accurate insulin delivery, enhance quality of life, and are preferred over vial and syringe (Robertson, Glazer, & Campbell, 2000).

Another insulin delivery device for patients on replacement therapy is continuous subcutaneous insulin infusion using an insulin pump. These battery-operated devices can be preprogrammed to deliver continuous microdoses of rapid-acting insulin by pulses termed “basal rate.” Boluses of larger amounts of insulin are taken by the patient as needed to cover the carbohydrate in meals or snacks and to

counteract hyperglycemia. Although they are used more often for patients with type 1 diabetes, these devices provide a more physiological delivery of insulin and can be an option for some patients with type 2 diabetes on insulin replacement therapy who need more flexibility and greater delivery choices. Several of these devices are available with various insulin delivery features.

Inhaled insulin was briefly available (Exubera; Pfizer Inc., New York, NY) to patients but has been withdrawn from the marketplace. Clinical trials are ongoing with other inhaled insulins.

Conclusions and summary

Nurse practitioners and other clinicians need to be aware of the urgent need for helping more patients to optimize their glycemic control, which can only be accomplished by normalizing blood glucose throughout the day. Treatment should be based on the pathophysiology of the disease and needs to consider factors such as expected hemoglobin A_{1c} decrease, patient tolerance, effect on comorbidity such as lipid levels, and cost. As beta-cell secretion declines, insulin is the most effective hypoglycemic agent that given in appropriate dosage, can allow any patient to reach desired glycemic targets. Appropriate counseling and patient education, coupled with use of insulin analogs, delivery devices, and treatment regimens, can help overcome many of the traditional barriers to insulin therapy.

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