Initiating Insulin Therapy in Patients with Type 2 Diabetes: A Practical Approach

R Cooppan

Citation

R Cooppan. *Initiating Insulin Therapy in Patients with Type 2 Diabetes: A Practical Approach*. The Internet Journal of Internal Medicine. 2006 Volume 6 Number 2.

Abstract

Because most patients with type 2 diabetes will ultimately require insulin, understanding when and how to use insulin therapy is a vital part of diabetes care. Unfortunately, insulin therapy is often delayed, due in part to the reluctance of both patients and health care providers to use insulin. Some health care providers may not be aware of when and how to initiate insulin therapy and what insulin regimens may be most appropriate for an individual patient. Modern insulin therapies such as rapid-acting insulin analogs, long-acting insulin analogs, and biphasic (premixed) insulin analogs are likely to improve patient care by providing more physiologic insulin time-action profiles, greater glycemic control, and greater convenience than human insulin preparations. This article reviews data on newer insulin therapies and discusses how to use these therapies to best treat typical patients with type 2 diabetes.

INTRODUCTION

Due to the progressive nature of type 2 diabetes, most patients with this disease ultimately require insulin therapy.[1,2] The increasing prevalence of type 2 diabetes suggests that more and more patients will be candidates for insulin, which is the most effective therapy for diabetes currently available.[3] The goal of insulin therapy is to mimic the body's natural insulin response while avoiding both hyperglycemia and hypoglycemia. In individuals without diabetes, serum insulin levels peak within 15 to 45 minutes of a meal, and return to basal levels within 1 to 3 hours, limiting postprandial glucose excursions. Basal secretion of insulin occurs at a low rate between meals. Insulin therapy that can reproduce this normal physiology as closely as possible would control both fasting glucose and postprandial glucose, bringing patients closer to normal glucose homeostasis.

Patients can be reluctant to use insulin due to concerns about pain with injections, complex treatment regimens, hypoglycemia, and weight gain.[4] In addition, clinicians may be unsure when to begin insulin treatment, how to choose an insulin regimen, whether to continue therapy with oral antidiabetic drugs (OADs) in patients beginning insulin, how to minimize hypoglycemia, how to set glycemic targets, how to encourage self-monitoring of blood glucose (SMBG), and how to overcome patient concerns regarding insulin therapy. This article will address each of these issues by reviewing recent data on insulin therapy and discussing insulin management using a practical, case-based approach.

CONVENTIONAL HUMAN INSULIN THERAPIES

Older, conventional human insulin therapies include Neutral Protamine Hagedorn (NPH), an intermediate-acting insulin used as basal replacement, and short-acting regular human insulin traditionally used as bolus therapy. These treatments have significant drawbacks that may complicate insulin use in patients with type 2 diabetes. One of their principal limitations is related to their inability to closely mimic physiologic insulin secretion patterns. The ideal basal therapy should provide a constant and predictable level of plasma insulin and should be long-acting. In contrast, NPH produces a distinct insulin peak 4 to 10 hours after subcutaneous injection,[5,6,7] has a slow onset of action (2 to 4 hours) and a short duration of action (10 to 16 hours),[5,6,7] and exhibits considerable variability in absorption, as shown in Table 1.[8,9]

Figure 1

Table 1: Onset, Peak, and Duration of Action of Insulin Therapies,,,,,,,,

Insulin	Onset	Peak	Effective Duration
Conventional insulin therapies			
Regular human insulin	30-60 min	2-3 h	5-8 h
NPH	2-4 h	4-10 h	10-16 h
Premixed NPH/regular human insulin (70% NPH/30% regular human insulin)	30-60 min	Dual	10-16 h
Rapid-acting insulin analogs			
Insulin lispro	5-15 min	30-90 min	<5 hours
Insulin aspart	5-15 min	30-90 min	<5 hours
Insulin glulisine	20 min	90 min*	5.3 h*
Long-acting insulin analogs			
Insulin glargine	2-4 h	4 h (peak not pronounced)	Up to 24 h
Insulin detemir	0.8-2 h	3-9 h (peak not pronounced)	Up to 24 h
Premixed insulin analogs			
75% NPL/25% lispro	5-15 min	Dual	10-16 h
50% NPL/50% lispro	5-15 min	Dual	10-16 h
70% insulin aspart protamine/ 30% aspart	5-15 min	Dual	10-16 h

*Median values. NPH = Neutral Protamine Hagedorn; NPL = Neutral Protamine Lispro

The ideal bolus insulin should provide a rapid rise in serum insulin levels with a peak insulin concentration 30 to 45 minutes after the meal and then fall rapidly to basal levels over the next 2 to 3 hours. However, regular human insulin is relatively slowly absorbed, providing peak insulin levels 2 to 3 hours after injection (Table 1). As a result, injecting regular human insulin at mealtimes can result in high blood glucose concentrations within 1 to 2 hours of a meal and an increased risk of late hypoglycemia.[16] Therefore, patients need to administer regular insulin 30 to 45 minutes before meals, which can be inconvenient and at times difficult to predict. Like NPH, regular human insulin also exhibits significant day-to-day variability in absorption.[6,17]

The most physiologic insulin regimen is basal-bolus therapy with multiple daily injections, with 1 to 2 injections of a basal insulin and an injection of a prandial insulin with each meal. Alternatively, an insulin pump can be used to meet both basal and prandial insulin needs. For patients who desire a simpler, more convenient therapy to cover both FPG and PPG, premixed insulin preparations that include NPH and regular human insulin in various proportions have been used. These preparations facilitate administration by eliminating the need to manually mix insulins. However, premixed human insulins have the same limitations as regular human insulin: they must be administered 30 to 45 minutes before the meal due to the slow onset of action. In addition, the slow onset of action of conventional premixed insulin may result in an increased risk of hypoglycemia.[18]

INSULIN ANALOG THERAPIES

Long-, rapid-acting and premixed insulin analogs have overcome many of the limitations of older insulin therapies. Both rapid-acting and long-acting insulin analogs were developed using recombinant DNA technology to produce slight modifications to the structure of native human insulin. Human insulin is a polypeptide consisting of two chains: the A chain, which includes 21 amino acids, and the B chain, which includes 30 amino acids.[16]All rapid-acting analogs, such as insulin lispro, insulin aspart, and insulin glulisine, have been created by substituting a different amino acid for the amino acid at either position 28 and/or 29 on the B-chain of insulin, respectively while asparagine also replaces lysine as position B3 in glulisine. In the basal insulin analog, insulin detemir, the final amino acid on the A-chain has been changed from asparagine to glycine, and a fatty acid chain has been attached to the amino acid at position 29 in the B-chain. The fatty acid chain acts as a depot that slowly releases the insulin into the blood stream. In contrast, insulin glargine includes substitutions at the terminal amino acid on the A-chain and two new amino acids at position 30 on the B-chain. By creating slight modifications to the structure of native human insulin, these newer insulin therapies exhibit more physiologic pharmacokinetic profiles, offer improved opportunities for intensive insulin therapy, and may facilitate hemoglobin A1C (HbA_{1C}) goal achievement.[6,16]

RAPID-ACTING INSULIN ANALOGS

In 1996, the first insulin analog, insulin lispro, was introduced in the United States.[19]Today, insulin lispro and two other rapid-acting insulin analogs (insulin aspart and insulin glulisine) offer significant advantages compared to regular human insulin. These agents are more rapidly absorbed after subcutaneous injection, producing earlier and higher peak insulin levels compared to regular human insulin (Table 1).[5,6,7,14,15] In general, injection of these rapid-acting agents results in higher peak insulin concentrations in half the time of equivalent doses of regular human insulin.[6] They also have a shorter duration of action than regular human insulin.[6] In general, rapid-acting insulin analogs can be administered within 15 minutes of starting a meal, making them considerably more convenient than regular human insulin (which, as noted, must be administered 30 to 45 minutes before a meal). All three rapid-acting analogs have

been shown to be superior to regular human insulin in reducing postprandial hyperglycemia.[20,21,22] Insulin lispro and insulin aspart are also associated with a reduced incidence of severe hypoglycemia and nocturnal hypoglycemia in patients with type 2 diabetes compared with regular human insulin.[23,24,25] A large meta-analysis reported a 25% reduction in the frequency of severe hypoglycemia with insulin lispro compared with regular human insulin.[23]Another trial reported a 72% reduction in the incidence of nocturnal hypoglycemia with insulin aspart compared to regular human insulin in patients with type 1 diabetes.[25]In addition, patients using rapid-acting insulin therapies also report higher levels of treatment satisfaction than do patients using regular human insulin.[26]

INHALED INSULIN

Inhaled insulin (which is regular human insulin and not an analog) is another recently approved rapid-acting option for prandial glycemic control. Clinical trials have confirmed similar efficacy and hypoglycemic risk to regular human insulin injected subcutaneously in patients with either type 1 or type 2 diabetes.[27,28] Concerns regarding its long-term safety profile (particularly in patients with pulmonary disease) and its cost-effectiveness may limit its use, however; furthermore, patients requiring basal insulin would still need to administer injections.[29]

LONG-ACTING INSULIN ANALOGS

Although rapid-acting insulin analogs address the problem posed by the slow absorption of regular human insulin, their short duration of action precludes their use as basal therapies to control fasting plasma glucose (FPG) unless they are used in an insulin pump. However, two long-acting insulin analogs are now available, insulin glargine and insulin detemir. They offer significant advantages compared to NPH. Both long-acting analogs provide closer approximations of the basal insulin secretion pattern seen in healthy individuals. Both insulin glargine and insulin detemir provide constant, relatively flat plasma insulin levels and have longer durations of action than NPH (Table 1).[5,6,7,10,11,12,13] The time-action profiles of these analogs also exhibit significantly less within-subject variability in insulin absorption than NPH and both glargine and detemir can be administered once daily.[30,31] Clinical trials have demonstrated that insulin glargine and insulin detemir are associated with lower FPG levels, a more predictable time-action profile, and a reduced risk of nocturnal hypoglycemia compared with NPH.[31,32,33,34,35,36] In addition, insulin detemir is associated with less weight gain and has a more consistent blood glucose lowering effect than NPH insulin and insulin glargine.[33,34,35,36,37]

Several studies have compared the impact of adding long-acting insulin analogs or NPH to existing therapy in patients with type 2 diabetes inadequately controlled with oral antidiabetic drugs (OADs).[3,35,36,38]Both insulin glargine and insulin detemir have been evaluated in treat-to-target trials, in which patients experiencing poor control on oral agents received the basal insulin analog or NPH.[3,35,38]In these studies, insulin doses were actively titrated using a prespecified algorithm and plasma glucose monitoring to achieve a target FPG level of <100 mg/dL. These treat-to-target studies have shown that adding insulin glargine or insulin detemir effectively controls glycemia with less hypoglycemia, and, in the case of detemir, less weight gain, compared to NPH.[3,35]

In another clinical study, subjects who were not at target HbA_{1C} while taking 1 or 2 OADs were randomized to either 10 units of NPH insulin or insulin glargine at bedtime.[3] In this 24-week study, investigators used a physician-driven, weekly titration algorithm to adjust the insulin dose to achieve an FPG level <100 mg/dL. More than 55% of subjects treated with either insulin in this study achieved the target HbA_{1C} of ≤ 7.0%. However, a statistically significant reduction in the incidence of nocturnal hypoglycemia was observed in subjects using insulin glargine, and a greater percentage of patients using insulin glargine achieved target HbA_{1C} without documented nocturnal hypoglycemia (33% vs 27%).

In a similar treat-to-target study evaluating the efficacy of insulin detemir in patients inadequately controlled on oral agents, more than 70% of subjects who received insulin detemir or NPH achieved the target HbA_{1C} of ≤ 7.0%.[35]However, a significantly higher proportion of subjects treated with insulin detemir achieved target HbA_{1C} without hypoglycemia compared to NPH (26% vs 16%). Most notably, treatment with insulin detemir was associated with a significantly lower risk of overall and nocturnal hypoglycemia, and significantly less weight gain compared to NPH (1.2 kg vs 2.8 kg).

A recent treat-to-target study comparing insulin glargine and insulin detemir in patients who were not at goal on OADs reported that a similar percentage of patients using insulin detemir and insulin glargine achieved target HbA_{1C}.[36] The risk of overall and nocturnal hypoglycemia was also similar

between groups. However, patients using insulin detemir experienced significantly less weight gain compared to patients using insulin glargine (2.7 kg vs 3.5 kg).

BIPHASIC (PREMIXED) INSULIN ANALOG THERAPIES

Biphasic insulin analogs (also known as premixed insulin analogs) provide a convenient approach to covering both basal and prandial insulin requirements in one injection. Three biphasic insulin analogs are currently available in the US: biphasic insulin aspart 70/30 (BiAsp 30; 70% insulin aspart protamine suspension and 30% insulin aspart), biphasic insulin lispro 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro), and biphasic insulin lispro 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro). The protaminated component provides basal coverage, while the rapid-acting component provides prandial coverage. Unlike conventional human premixed insulin formulations, BiAsp 30 can be administered 15 minutes before or after meal initiation. However, the labeling for biphasic insulin lispro 75/25 and 50/50 state that they should be administered in the 15 minutes before a meal.[39]

Both BiAsp 30 and insulin lispro 75/25 provide effective control of FPG and postprandial glucose (PPG) while offering the convenience of fewer total daily injections compared to traditional basal-bolus therapy. These formulations provide better postprandial glycemic control with a reduced risk of hypoglycemia compared with premixed human insulin.[40,41,42,43,44] In addition, patients with type 2 diabetes inadequately controlled on OADs alone who add biphasic insulin analogs twice daily are more likely to achieve HbA_{1C} goals than patients using insulin glargine once daily, but with a slightly increased risk of minor hypoglycemia.[45,46,47] In 233 patients with type 2 diabetes initiating insulin therapy but continuing on metformin (± pioglitazone), 66% treated with BiAsp 30 BID and 40% treated with insulin glargine QD reached an HbA_{1C} <7% after 28 weeks.[47]In another study comparing twice-daily biphasic insulin lispro 75/25 to once-daily insulin glargine in patients continuing on metformin, 42% of insulin-naïve patients using insulin lispro 75/25 achieved an HbA_{1C} ≤ 7.0%, compared to 18% using insulin glargine.[45]However, the incidence of minor hypoglycemia was higher with the biphasic insulin analogs compared to insulin glargine, which is consistent with the improvement in glycemic control.[45,47]

In addition, in the 1-2-3 Study of 100 patients with type 2 diabetes inadequately controlled on oral agents with or without basal insulin, the use of BiAsp 30 once, twice, or three times daily enabled 41%, 70%, and 77% of patients to achieve an HbA_{1C} goal of <7.0% and 21%, 52%, and 60% of patients to achieve an HbA_{1C} goal of ≤ 6.5%.[48]

INITIATING INSULIN THERAPY

The initiation of insulin therapy is often inappropriately delayed in patients with type 2 diabetes. Although patients' concern about starting insulin therapy likely contributes to this delay, clinicians also may be reluctant to begin insulin due to concerns about the time required to educate patients about insulin therapy and an uncertainty about when and how insulin therapy should be initiated.

The decision to initiate insulin often depends on whether the patient is able to achieve the glycemic targets recommended by the American Diabetes Association (ADA) or the American College of Endocrinology (ACE)/American Association of Clinical Endocrinologists (AACE) with OADs or other diabetes medications. These organizations have established targets for HbA_{1C}, FPG, and PPG. For example, the ADA recommends an FPG target of 90 to 130 mg/dL, a PPG target of <180 mg/dL, and an HbA_{1C} target of <7.0% (Table 2).[49]The ACE/AACE guidelines are slightly more aggressive, recommending a FPG target of <110 mg/dL, a 2-hour PPG target of <140 mg/dL, and an HbA_{1C} target of ≤ 6.5%.[50]

Figure 2

Table 2: Glycemic targets recommended by the ADA and ACE/AACE.,

	ADA[49]	ACE/AACE[50]
FPG (mg/dL)	90-130 mg/dL	<110 mg/dL
PPG (mg/dL)	<180 mg/dL	<140 mg/dL
HbA1C (%)	<7.0%	≤6.5%

The ACE has published guidelines for managing patients with type 2 diabetes that include advice about when insulin therapy should be considered.[51] Central to these guidelines is an understanding of the importance of providing comprehensive coverage of both FPG and PPG. Although PPG excursions are a significant contributor to daytime hyperglycemia, past therapies for diabetes have focused on improving control of FPG, not PPG.[25]Evidence suggests that elevated PPG is a major risk factor for cardiovascular disease and affects the risk of morbidity and mortality associated with hyperglycemia.[52,53,54] Moreover, the contribution of PPG excursions to HbA_{1C} increases as

patients approach an HbA_{1C} <7%.[55] Therefore, as glycemic control improves with basal treatment, PPG coverage will be needed to reach an HbA_{1C} <7%.

Self-monitoring of blood glucose (SMBG) can be helpful in determining appropriate targets for therapy, when to initiate insulin therapy, and the most useful insulin regimen for a particular patient. It is particularly useful to monitor responses to therapy and to identify and treat glycemic excursions above or below target levels. Clinical experience suggests that SMBG is an important component of effective therapy.

WHEN TO INITIATE INSULIN THERAPY

Most patients with type 2 diabetes who are candidates for insulin therapy typically have experienced inadequate glycemic control on one or more OADs. Clinicians must decide whether to add another OAD or to initiate insulin in these instances. Because adding an OAD typically reduces HbA_{1C} by approximately 1% to 1.5%,[56] patients with HbA_{1C} levels ≥8.5% are candidates for insulin therapy since other agents will not reduce HbA_{1C} to goal levels.[51]According to ACE guidelines, insulin therapy should be initiated in all patients on one or more OADs with HbA_{1C} >8.5%.[51]The incretin mimetic exenatide is a new treatment option that also can be considered for patients inadequately controlled on metformin or a sulfonylurea. However, because treatment with exenatide only results in HbA_{1C} decreases of 0.8% to 1.0%,[57,58] it may not be an appropriate choice for patients with an HbA_{1C} level >10.0%.

For patients who have not yet received pharmacologic treatment for type 2 diabetes, insulin is a recommended option for patients with an HbA_{1C} ≥8.0% and should be initiated in individuals with an HbA_{1C} of >10%.[51]

WHAT TYPE OF INSULIN TO INITIATE

Many factors should be considered when selecting an insulin preparation to add to a modified OAD regimen (see next section). These include HbA_{1C}, FPG, and PPG levels; lifestyle and desire for flexibility; and time to teach and learn. Unless contraindicated, sensitizers are usually retained while secretagogues are only continued when basal insulin alone is added. Among the most important considerations are the results from the patient's SMBG log, if available. For example, patients who predominantly have elevated FPG levels are good candidates for basal insulin therapy, while patients who have both elevated FPG and PPG are likely candidates for premixed insulin or basal-bolus therapy. Most recently the FDA has approved the use of the oral dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin. By inhibiting DPP-4, an enzyme that inactivates glucagon-like peptide 1 (GLP-1), sitagliptin enhances the activity of native GLP-1, a hormone that increases glucose-stimulated insulin release, suppresses the increased glucagon secretion, slows gastric emptying and increases satiety.[59,60] Sitagliptin is approved as monotherapy when diet and exercise inadequately control blood glucose and can be used in combination with metformin or a thiazolidinedione. It is contraindicated in combination with a sulfonylurea or in patients with type 1 diabetes.

The patient's willingness to use insulin, ability to inject insulin, and calculate and titrate dosages, and lifestyle also should be considered (Table 3).[61] Patients who are overwhelmed by the prospect of using insulin therapy or who are opposed to multiple daily injections may be better candidates for basal insulin therapy or premixed insulin therapy than for basal-bolus therapy. Before initiating any insulin regimen, individualized blood glucose targets and titration schedules should be established to prevent hypoglycemia and excessive weight gain.

Figure 3

Table 3: A General Assessment Guide for Selecting and Starting an Insulin Regimen in Patients with Type 2 Diabetes.

Regimen	Glycemic Pattern	Patient Issues	Lifestyle (Nutrition, Activity, Schedule)
Basal Insulin + OADs	Predominantly elevated FPG FPG targets achieved with OADs or incretins	Feeling overwhelmed Resists insulin Fears injections Opposed to ≥2 injections	Has moderate carb intake at meals Seldom snacks or chooses small snacks (1-2 carb choices)
Premixed Insulin + OADs	Elevated PPG and FPG Blood glucose high all day	Feeling overwhelmed Opposed to >2 injections Opposed to taking midday injection Likes to snack but unwilling to inject for snacks	Has consistent meal times Has consistent carb intake Less than 10-12 h between breakfast and supper
Basal-Bolus Insulin	Elevated FPG and/or PPG	Desires "tight" control Willing to administer multiple injections Willing to test blood glucose 4 or more times each day Willing to inject for snacks >1 carbohydrate (if rapid-acting insulin)	Desires flexible schedule, food intake, and/or activity level Travels frequently with large changes in time zones Works rotating shifts Has different scheduled workdays vs days off

Adapted from Pearson J, Powers MA. Systematically initiating insulin: the staged diabetes management approach. *Diabetes Educ*. 2006;32(1 suppl):19S-28S.[61]

HOW TO INITIATE AND TITRATE INSULIN THERAPY

A variety of strategies for initiating and titrating insulin therapy in patients inadequately controlled on oral agents are currently used. Many patients will remain on OAD therapy once they begin insulin therapy. Continuing OADs has

several advantages because some, such as metformin and thiazolidinediones, are insulin sensitizers while others increase endogenous insulin secretion (sulfonylureas, meglitinides). For example, combining insulin with oral agents such as metformin can reduce the dose of insulin and decrease the amount of weight gain.[5] The decision to continue OADs after insulin is initiated often depends on the type of insulin administered and the type of OADs used. Additionally, in some patients, a GLP-1 analog such as exenatide may be appropriate. However, clinical experience with GLP-1 analogs is limited and combination therapy with insulin and exenatide is not approved by the FDA at this stage.

Results from SMBG logs can be particularly useful in monitoring and titrating insulin therapy. The ADA recommends that SMBG be performed 3 or more times daily in patients using multiple insulin injections.[49]Diabetes educators can help educate patients about SMBG techniques, how to adjust food intake based on the data, and how to use SMBG data to adjust therapy.

BASAL INSULIN THERAPY

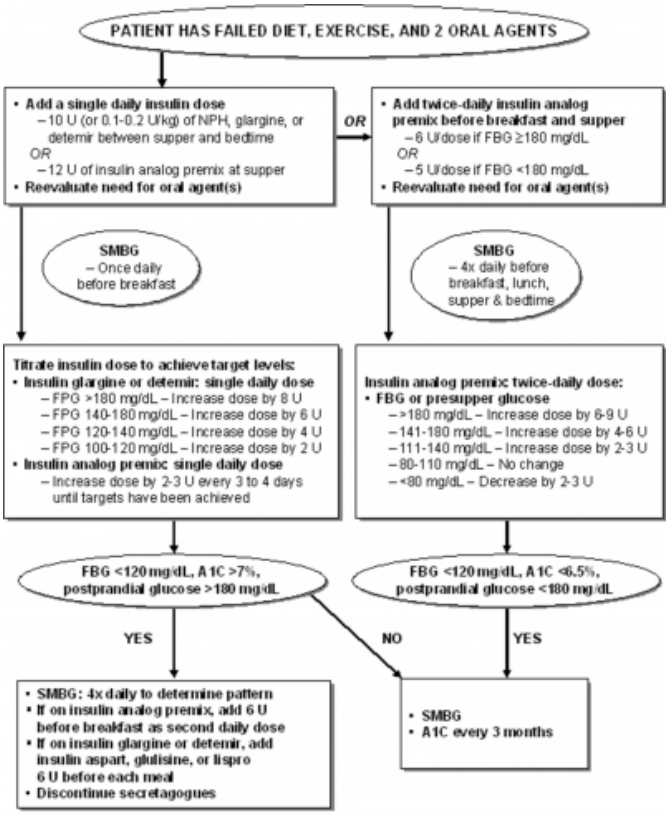
For patients initiating basal therapy who have been inadequately controlled on OADs, the initial dose is typically 10 units/day or 0.1 to 0.2 units/kg/day (Figure 1).[11,62,63] Initially, basal therapies are usually administered as a single dose in the evening. Where necessary, insulin detemir and NPH insulin also may be given in 2 doses: 1 dose in the morning and 1 dose in the evening. The dose can be titrated in 1-, 2-, or 3-unit increments until target FPG levels are achieved. When initiating insulin, it is best to start low and increase the dose gradually until the target is reached. This minimizes the risk of hypoglycemia. In general, overweight patients require higher doses.

In the treat-to-target study of insulin glargine, the dose was adjusted weekly from the starting dose of 10 units to achieve FPG <100 mg/dL.[3] Insulin doses in the treat-to-target study of insulin detemir were adjusted to enable participants to achieve pre-breakfast and pre-supper FPG targets of <108 mg/dL (≤ 6.0 mmol/L).[35]

Insulin secretagogues are often used with basal insulin therapy to cover postprandial glucose excursions. Postprandial coverage is provided by the rapid-acting component of premixed insulin therapies; therefore, insulin secretagogues and -glucosidase inhibitors are usually discontinued when premixed insulin therapy is initiated.[64] However, treatment with metformin and/or thiazolidinediones is often continued to address patients' underlying insulin resistance.

Figure 4

Figure 1: Dosing and Monitoring of Insulin Therapy.



SMBG = self-monitoring of blood glucose; FPG = fasting plasma glucose; A1C = HbA_{1C}.

To convert values for glucose from mg/dL to mmol/L, multiply by 0.05551.

Adapted from Brunton S, et al. Type 2 diabetes: the role of insulin. *J Fam Pract*. 2005;54(5 suppl):445-451.[63]

BASAL-BOLUS THERAPY

Because of the progressive nature of type 2 diabetes, insulin therapy will likely require intensification. Many patients who begin insulin therapy with a basal insulin who eventually require postprandial control will either need to add a bolus insulin at mealtimes (and potentially beginning basal-bolus therapy) or switch to premixed insulin therapy. In contrast, patients who begin premixed insulin therapy once daily at dinner can add a second dose in the morning to achieve greater glycemic control. Due to the favorable pharmacokinetic advantages, a third injection of a premixed insulin analog (but not premixed human insulin 70/30) can also be added at lunch if necessary.[48]

Although basal-bolus therapy may be more challenging and time consuming to initiate and teach, it provides the most physiologic insulin profile and flexibility for the patient. Basal-bolus therapy involves multiple daily injections or an insulin pump can be used. Approximately 50% of the total

daily insulin dose should be a basal insulin.[61] The remaining 50% of the total daily dose should be administered as a bolus, or prandial, insulin therapy, divided between meals. Patients who are using OADs and beginning basal-bolus therapy often continue therapy with metformin or insulin sensitizers. However, as previously mentioned, a premixed insulin analog BID can be just as affective as basal-bolus therapy for some patients.[65]

PATIENT PROFILES

The following cases illustrate how to apply the principles of insulin therapy to patients similar to those seen in typical practices.

CASE 1

A 48-year-old man with a 5-year history of type 2 diabetes has an HbA_{1C} of 7.8% while using metformin 1000 mg BID, glyburide 10 mg/d, and rosiglitazone 4 mg BID. His meals are irregular and he appears to be overwhelmed by the possibility that he may need insulin therapy. He fears injections and the complexity of insulin therapies. According to his SMBG results, his postprandial readings are <180 mg/dL with his current agents but his FPG levels range from 140 to 160 mg/dL.

Possible treatment options for this patient include a basal insulin analog, NPH, or a premixed insulin analog. However, the patient resists insulin therapy, explaining that he feels like he has failed in managing his disease and that he is concerned about hypoglycemia, injections, and weight gain.

OVERCOMING PATIENT CONCERNS

Providing comprehensive education may be the best way to address patient concerns about insulin therapy. Because educating patients about insulin can be time-consuming, including a registered dietician or a diabetes educator may be very useful.

Perhaps one of the most important topics in patient education is to explain that type 2 diabetes is a progressive disease. It is important that the patient understands the natural history of type 2 diabetes and that most patients will ultimately require insulin therapy to achieve and maintain glycemic goals. This should be communicated to patients early in the management of their disease. The benefits of intensive glycemic control with insulin therapy should also be clearly communicated, including the potential for a reduced risk of diabetes complications. Increased patient involvement in management of their diabetes may also be beneficial, not only in overcoming barriers but also in achieving tight glycemic control. A larger, multicenter study showed that patient titration of basal insulin according to a set algorithm resulted in greater reductions in HbA_{1C} (-1.22% vs. -1.08%) and fasting blood glucose levels (-62 mg/dL vs. -57 mg/dL) compared to physician titration.[66] Patients who fear hypoglycemia should be assured that the risk of hypoglycemia in patients with type 2 diabetes is less than the risk observed in patients with type 1 diabetes, and that the risk can be minimized by making small adjustments in therapy as needed and avoiding missing meals or undertaking exercise if prandial insulin has been injected. However, all patients should be educated about the signs and symptoms of hypoglycemia and steps they can take to prevent and treat hypoglycemic episodes.

One of the most common patient concerns is needle phobia. Patients who fear injections may be confusing the larger needles designed for intravenous access with the small (31G) coated needles used for insulin administration. The differences between these two types of needles should be stressed. Concerned patients should be educated about modern insulin delivery systems that are more convenient than vials and syringes, such as pens, dosers, and pumps.[4] For example, compared to syringes, insulin pens have been found to be faster and easier to use, easier to teach patients how to use, were associated with improved patient acceptance and adherence, and provided more accurate dosing.[4,67,68,69,70] A recent study also demonstrated that insulin pens were associated with improved accuracy, precision, and reduced training staff utilization and were preferred by patients compared to vials and syringes.[71] Another recent study that compared the FlexPen® (Novo Nordisk) and the OptiClik® (Sanofi-Aventis) devices reported that the FlexPen was easier to use, easier to learn how to use, less prone to errors, and preferred by more patients.[72] The FlexPen also may be easier to use in patients with mild visual deficits and impaired dexterity.

Most insulin therapies are associated with mild-to-moderate weight gain. However, changes in weight can be addressed by moderate reductions in caloric intake and increased physical activity. In addition, new treatment options such as insulin detemir have been shown to be associated with less weight gain compared to insulin glargine and NPH, which may be appealing to some patients.[33,34,35,36]

TREATMENT

The patient agrees to initiate insulin after a discussion of the benefits and risks of insulin regimens. Because his FPG

levels are elevated while his PPG levels are adequately controlled, and to avoid multiple daily injections, he initiates insulin therapy with a long-acting basal analog at a dose of 10 units at bedtime and continues OAD therapy. He is instructed to titrate therapy to achieve FPG levels of 90 mg/dL to 130 mg/dL. Several months later, his SMBG results indicate that his FPG and PPG are well controlled. His HbA_{1C} is now 6.9%. Further decreases in HbA_{1C} may require addition of a prandial insulin.

CASE 2

A 60-year-old woman takes metformin 1000 mg BID, repaglinide 4 mg with meals, and pioglitazone 45 mg/d. She works full time and her meals are consistent in both timing and portion sizes. She complains of nocturia, polyuria, and polyphagia and her body weight has increased by 15 lbs in the past 6 months. Her HbA_{1C} is 8.2%; her FPG levels range from 160 to 180 mg/dL; and several of her post-supper glucose readings in her SMBG log have been >300 mg/dL.

ASSESSMENT

This patient's glycemic control is inadequate with combination therapy with metformin, repaglinide, and pioglitazone. Her FPG levels are high and her postprandial levels are markedly abnormal. In addition, her HbA_{1C} level suggests that her hyperglycemia may be related to high postprandial glucose excursions. It is time to initiate insulin therapy in this patient. Before initiating insulin in patients poorly controlled on OADs, however, practitioners must define blood glucose targets, identify the insulin regimen that might be the most appropriate for this patient, and decide whether the patient should remain on their OADs.

TREATMENT

To determine which insulin regimen will most likely help this patient achieve her glucose targets and which insulin regimen will be most acceptable to the patient, it is important to consider the patient's symptoms, duration of diabetes, blood glucose patterns, current HbA_{1C} level, comorbid conditions, treatment preferences, and lifestyle. Because the patient has a remarkably high postprandial level, particularly following the evening meal (and wishes to minimize injections), initiating a premixed insulin analog might be most appropriate.

Since this patient's FPG levels exceed 180 mg/d, she begins therapy with 12 units of BiAsp30 before supper. She discontinues therapy with repaglinide because the biphasic therapy can cover her postprandial glucose needs, but continues therapy with metformin and pioglitazone. In a recent study, more than 75% of patients who were inadequately controlled on optimal doses of metformin and pioglitazone achieved their target HbA_{1C} after receiving titrated doses of BiAsp 30 twice daily.[73] She also receives dietary and exercise counseling to help her with food choices and weight control.

FOLLOW-UP

Several months later, the patient returns to the office and shows her SMBG results. Her pre-breakfast FPG, post-supper PPG, and bedtime readings are at goal, but all other PPG levels are elevated. Her post-breakfast levels range from 200 to 280 mg/dL. A pre-breakfast dose of BiAsp 30 was added to address her elevated post-breakfast glucose and help control her daytime glycemic levels. At the patient's next visit, her SMBG log indicates that she has achieved good glycemic control. Her HbA_{1C} is 6.8%. Regular follow-up will continue to be important. The patient has also lost 7 pounds due to better food choices and a walking program.

CONCLUSIONS

Insulin analogs have more physiologic time-action profiles, are more convenient, and may provide improved glycemic control with fewer hypoglycemic episodes compared to conventional human insulin therapies. Rapid-acting and premixed insulin analogs can be administered at mealtimes, instead of 30 to 45 minutes before the initiation of a meal, and limit PPG excursions compared to regular human insulin, while basal insulin therapies can provide more constant and predictable glycemic control with a lower potential for hypoglycemia compared to NPH. In addition, insulin detemir, causes less weight gain compared to NPH.

The successful use of insulin therapies requires an understanding of when and how to initiate insulin treatment in patients with type 2 diabetes. An understanding of how to individualize insulin therapy and how to educate patients about the role of insulin therapy in the management of their disease is also a critical component of the optimal management of patients with diabetes. Initiating insulin therapies may allow patients to attain and maintain glycemic targets and reduce their risk of complications.

ACKNOWLEDGEMENTS

The author would like to thank Novo Nordisk for funding that helped support the preparation of this manuscript and Nicole Cooper for writing and editorial assistance.

CORRESPONDENCE TO

Ramachandiran Cooppan, MD Joslin Diabetes Center 1 Joslin Place Boston, MA 02215 Phone: 617-732-2675 Fax: 617-732-2452 E-mail: chan.cooppan@joslin.harvard.edu rcooppan@comcast.net

References

1. U.K. Prospective Diabetes Study Group. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes. 1995;44:1249-1258.
2. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA. 1999;281:2005-2012.
3. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26:3080-3086.
4. Meece J. Dispelling myths and removing barriers about insulin in type 2 diabetes. Diabetes Educ. 2006;32:9S-18S.
5. DeWitt DE, Dugdale DC. Using new insulin strategies in the outpatient treatment of diabetes: clinical applications. JAMA. 2003;289:2265-2269.
6. Hirsch IB. Insulin analogues. N Engl J Med. 2005;352:174-183.
7. Kamal AD, Dixon AN, Bain SC. Safety and side effects of the insulin analogues. Expert Opin Drug Safety. 2006;5:131-143.
8. Galloway JA, Spradlin CT, Nelson RL, Wentworth SM, Davidson JA, Swarner JL. Factors influencing the absorption, serum insulin concentration, and blood glucose responses after injections of regular insulin and various insulin mixtures. Diabetes Care. 1981;4:366-376.
9. Heinemann L. Variability of insulin absorption and insulin action. Diabetes Technol Ther. 2002;4:673-682.
10. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care. 2005;28:1107-1112.
11. Levemir® (insulin detemir [rDNA origin] injection) [product information]. Princeton, NJ: Novo Nordisk; 2005.
12. Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T. Time-action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304. Diabet Med. 1999;16:332-338.
13. Lantus® (insulin glargine [rDNA origin] injection) [product information]. Kansas City, MO: Aventis Pharmaceuticals; 2004.
14. Becker RHA, Frick AD, Burger F, Scholtz H, Potgieter JH. A comparison of the steady-state pharmacokinetics and pharmacodynamics of a novel rapid-acting insulin analog, insulin glulisine, and regular human insulin in healthy volunteers using the euglycemic clamp technique. Exp Clin Endocrinol Diabetes. 2005;113:292-297.
15. Cox SL. Insulin glulisine. Drugs Today (Barc). 2005;41:433-440.
16. Vazquez-Carrera M, Silvestre JS. Insulin analogues in the management of diabetes. Methods Find Exp Clin Pharmacol. 2004;26:445-461.
17. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. Diabetes. 1994;43:396-402.
18. Culy CR, Jarvis B. Management of diabetes mellitus: defining the role of insulin lispro MIX75/25 (Humalog® Mix75/25). Dis Manage Health Outcomes. 2001;9:711-730.
19. Tanenberg RJ. Transitioning pharmacologic therapy from oral agents to insulin for type 2 diabetes. Curr Med Res Opin. 2004;20:541-553.
20. Anderson JH, Jr., Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. Diabetes. 1997;46:265-270.
21. Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. Diabetes Care. 1999;22:801-805.
22. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care. 2004;27:2363-2368.
23. Brunelle RL, Llewelyn J, Anderson JH Jr, Gale EA, Koivisto VA. Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. Diabetes Care. 1998;21:1726-1731.
24. Chapman TM, Noble S, Goa KL. Insulin aspart: A review of its use in the management of type 1 and 2 diabetes mellitus. Drugs. 2002;62:1945-1981.
25. Heller S. Reducing hypoglycaemia with insulin analogues. Int J Obes. 2002;26(suppl 3):S31-S36.
26. Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with Type 1 diabetes. Diabet Med. 2003;20:626-634.
27. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2005;143:549-558.
28. Skyler JS, Weinstock RS, Raskin P, et al. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. Diabetes Care. 2005;28:1630-1635.
29. Mayor S. Inhaled insulin no longer recommended as routine diabetes treatment. BMJ. 2006;333:14.
30. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes. 2000;49:2142-2148.
31. Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes. 2004;53:1614-1620.
32. Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care. 2001;24:631-636.
33. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab. 2005;7:56-64.
34. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. [Correction appears in Raslova K, et al. Diabetes Res Clin Pract. 2006;72:112]. Diabetes Res Clin Pract. 2004;66:193-201.
35. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as

add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006;29:1269-1274.
36. Rosenstock J, Davies M, Home PD, Larsen J, Tamer SC, Schernthanr G. Insulin detemir added to oral anti-diabetic drugs in type 2 diabetes provides glycemic control comparable to insulin glargine with less weight gain [abstract]. Diabetes. 2006;55(suppl 1):A132.
37. Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T. Insulin detemir and insulin glargine: similar time-action profiles in subjects with type 2 diabetes [abstract]. Diabetes. 2006;55(suppl 1):A76.
38. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia. 2006;49:442-451.
39. Humalog® Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection [rDNA origin]) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2005.
40. Marre M. Before oral agents fail: the case for starting insulin early. Int J Obes Relat Metab Disord. 2002;26(suppl 3):S25-S30.
41. Brange J, Volund A. Insulin analogs with improved pharmacokinetic profiles. Adv Drug Deliv Rev. 1999;35:307-335.
42. Roach P, Trautmann M, Arora V, Sun B, Anderson JH Jr, Mix50 Study Group. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin-protamine formulations, insulin lispro Mix25. Clin Ther. 1999;21:523-534.
43. Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients. Diabet Med. 2002;19:393-399.
44. Boehm BO, Vaz JA, Brondsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med. 2004;15:496-502.
45. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004;26:2034-2044.
46. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with type 2 diabetes. Diabet Med. 2005;22:374-381.
47. Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care. 2005;28:260-265.
48. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1-2-3 study). Diabetes Obes Metab. 2006;8:58-66.
49. American Diabetes Association. Standards of medical care in diabetes - 2006. Diabetes Care. 2006;29(suppl 1):S4-S42.
50. American College of Endocrinology. American College of Endocrinology consensus statement on guidelines for glycemic control. Endocr Pract. 2002;8(suppl 1):5-11.
51. Davidson JA, Blonde L, Jellinger PS, Lebovitz HE, Parkin CG. Road map for the prevention and treatment of type 2 diabetes. Available at: http://www.aace.com/meetings/consensus/odimplementation/roadmap.pdf. Accessed August 1, 2006.
52. DECODE Study Group on behalf of the European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care. 2003;26:688-696.
53. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the diabetes intervention study, 11-year follow-up. Diabetologia. 1996;39:1577-1583.
54. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. Eur Heart J. 2004;25:10-16.
55. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care. 2003;26:881-885.
56. Nathan DM. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med. 2002;347:1342-1349.
57. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28:1083-1091.
58. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28:1092-1100.
59. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696-1705.
60. Gallwitz B. Glucagon-like peptide-1-based therapies for the treatment of type 2 diabetes mellitus. Treat Endocrinol. 2005;4:361-370.
61. Pearson J, Powers MA. Systematically initiating insulin: the staged diabetes management approach. Diabetes Educ. 2006;32(1 suppl):19S-28S.
62. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003;289:2254-2264.
63. Brunton S, Carmichael B, Funnell M, Lorber D, Rubin R, Rakel R. Type 2 diabetes: the role of insulin. J Fam Pract. 2005;54(5 suppl):445-451.
64. Rolla AR, Rakel RE. Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. Clin Ther. 2005;27:1113-1125.
65. Liebl A, Prager R, Kaiser M, Binz K, Gallwitz B. Biphasic insulin aspart 30 (BIAsp30), insulin detemir (IDet) and insulin aspart (IAsp) allow patients with type 2 diabetes to reach A1C target: the PREFER study [abstract]. Diabetes. 2006;55(suppl 1):A123.
66. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. Diabetes Care. 2005;28:1282-1288.
67. Bohannon NJ. Insulin delivery using pen devices. Simple-to-use tools may help young and old alike. Postgrad Med. 1999;106:57-64, 68.
68. Rubin RR, Peyrot M. Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diabetes Care. 2004;27:2495-2497.
69. Bohannon NJ, Ohannesian JP, Burdan AL, Holcombe

JH, Zagar A. Patient and physician satisfaction with the Humulin®/Humalog® Pen, a new 3.0-mL prefilled pen device for insulin delivery. Clin Ther. 2000;22:1049-1067.
70. Korytkowski M, Bell D, Jacobsen C, Suwannasari R. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin Ther. 2003;25:2836-2848.
71. Schwartz S, Khutoryansky N, Braceras R. FlexPen® demonstrates improved accuracy, precision, preference and reduced resource utilization in patients with type 2 diabetes mellitus when compared to vial/syringe [abstract]. Diabetes. 2006;55(suppl 1):A101.
72. Asakura T, Seino H. Handling and safety of two insulin injection pens (FlexPen® and OptiClik®) in insulin-nalve type 2 diabetes patients [abstract]. Diabetes. 2006;55(suppl 1):A457.
73. Raskin P, Braceras R, Schwartz S, Chaykin L, Pei-Ling C, Wynne A. Over 75% of patients with type 2 diabetes reached target A1C by adding biphasic insulin aspart 70/30 to optimized metformin and pioglitazone treatment [abstract]. Diabetes. 2006;55(suppl 1):A131.

Author Information

Ramachandiran Cooppan, MD, FRCP(C), FACE
Senior Staff Physician, Joslin Diabetes Center