Practical Approaches to Using Insulin Analogs and Premixed Insulin Analogs in Patients with Type 2 Diabetes

An educational activity certified for physicians, pharmacists, nurses, and dietitians.

This continuing education activity can also be completed online at *www.MedEdToday.com/practical*.

Program Goal

The goal of this program is to provide theoretical and practical knowledge to healthcare providers regarding the use of insulin analogs and premixed insulin analogs in patients with type 2 diabetes.

Target Audience

This activity is intended for physicians, pharmacists, nurses, and dietitians who care for patients with type 2 diabetes.

Educational Objectives

- Review the prevalence and progressive nature of diabetes and the associated economic implications.
- Discuss the importance of glycemic control in type 2 diabetes and current strategies for achieving it.
- Explain how and when to initiate insulin for type 2 diabetes, including advantages and potential barriers.
- Compare different insulin formulations and regimens for type 2 diabetes, and discuss their appropriateness for different patient types.
- Review recent advances in insulin technology and the use of diabetes-care teams.

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Release date: October 16, 2006
Expiration date: October 16, 2008

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This publication is supported by an educational grant from Novo Nordisk Inc.

Published by Scherer Clinical Communications, 117 West Prospect Street, Hopewell, NJ 08525.

Printed in USA

October 2006

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Introduction

Overview

Diabetes is a debilitating and costly disease that is at epidemic levels in the United States. In 2005, a total of 20.8 million Americans, or 7% of the population, were estimated to have diabetes.[1] Ninety to 95% of these individuals have type 2 diabetes. Among adults 20 years or older, the prevalence of diabetes has increased from 8.7% in 2002 to 9.6% in 2005.[1,2] In the United States, the total (direct and indirect) costs attributable to diabetes were estimated to be $132 billion in 2002, and diabetes management was estimated to account for more than 10% of US healthcare costs.[3] These figures likely underestimate the true cost of the disease since they do not take into account factors such as pain and suffering, care provided by unpaid caregivers, and services used at higher rates by diabetics than nondiabetics (eg, podiatric, dental, and optometry services). In addition to the increasing number of Americans with diabetes, it is now estimated that another 41 million Americans have prediabetes, based on the revised definition of this condition by the American Diabetes Association (ADA).[1]

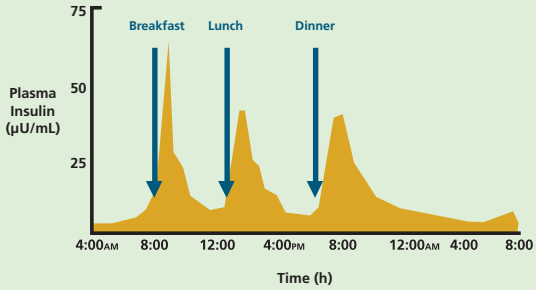
Patients with type 1 diabetes require insulin from the time of initial diagnosis, and the majority of patients with type 2 diabetes eventually require insulin for optimal glycemic control.[4] Due to the progressive nature of type 2 diabetes, it is imperative that healthcare professionals and patients with diabetes be aware of the benefits and safety of insulin, as well as new advances in insulin formulations and delivery systems. Insulin is the most effective therapy for diabetes, and has an excellent safety and tolerability profile when dosed properly.[5] Insulin analogs and premixed analogs have overcome many of the shortcomings of the older human insulin formulations.[6-9] The aim of this monograph is to describe practical approaches to initiating therapy with insulin analogs and premixed insulin analogs in patients with type 2 diabetes. This activity will explore the circumstances under which insulin treatment may be initiated, along with strategies for selecting the insulin dose and formulation, and adjustment of the regimen.

Contributors to Hyperglycemia

In individuals without diabetes, hepatic glucose production and output are limited primarily by basal insulin secretion, while large peaks in insulin secretion occur with meals (Figure 1). Diabetes is usually diagnosed by a fasting plasma glucose (FPG) ≥126 mg/dL, where *fasting* is defined as no caloric intake for at least 8 hours.[10] The diagnosis may also be made by a random plasma glucose ≥200 mg/dL in the presence of symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) or a 2-hour plasma glucose ≥200 mg/dL during a 75-gram oral glucose tolerance test (OGTT). In all cases, the diagnosis must be confirmed on a separate day unless unequivocal symptoms of hyperglycemia are present.[10]

The long-term (2–3 months) impact of hyperglycemia on glycemic control is best measured via A1C, which is a function of both fasting and postprandial glucose (PPG) exposure. Normal A1C is ≤6% and corresponds to an average blood glucose (BG) level of ≤135 mg/dL. On average, an increase of 1% in A1C corresponds to an increase in mean plasma glucose of ~35 mg/dL.[10,11]

Figure 1. Physiological Serum Insulin Secretion Profile in Nondiabetics



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Although most patients with diabetes monitor and aim treatment to achieve fasting glucose targets, PPG excursions (ie, high BG levels after meals) contribute substantially to overall diurnal hyperglycemia.[12] Monnier and colleagues[12] showed that among noninsulin-using patients with type 2 diabetes who were poorly controlled on 2 oral agents, PPG excursions accounted for most of the elevation of A1C in patients with mild or moderate hyperglycemia (A1C ≤8.4%), whereas fasting glycemic excursions were more important among those with severe disease (ie, A1C >8.4%). Thus, as patients get closer to their target A1C levels, elevations in PPG have a greater role in glycemic control compared with fasting BG.[12] In addition, analysis of data from the Third National Health and Nutritional Examination Survey (NHANES III) suggests that PPG excursions may be common even in patients who have good overall glycemic (A1C) control.[13]

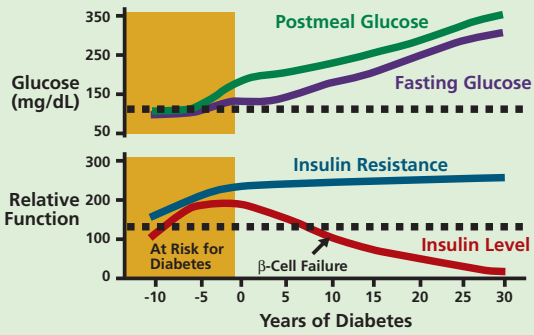
Other studies have examined the clinical implications of PPG excursions. Definitive data on PPG are not available, but postchallenge glucose data have suggested that they are associated with an increased risk of cardiovascular disease and death.[14,15] The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) was a multinational project that analyzed data from 13 prospective European cohort studies.[15] DECODE showed that high BG concentrations 2 hours after a 75-gram OGTT are associated with an increased risk of death, independent of fasting BG levels. The results of DECODE suggest that these 2-hour PPG concentrations are better predictors of mortality than fasting BG. Therefore, both fasting and PPG excursions should be considered in the management of diabetes.

Why Insulin?

Type 2 Diabetes Is a Progressive Disease

In type 1 diabetes, endogenous insulin secretion is virtually absent via autoimmune-mediated destruction of pancreatic β-cells, although some patients continue to produce residual insulin for varying periods.[6] In contrast, in type 2 diabetes, β-cell deterioration occurs progressively over many years; eventually the pancreas cannot synthesize and secrete sufficient insulin to meet the demands of insulin-resistant patients (Figure 2). Although secretagogues can augment insulin secretion, and sensitizers can enhance the action of endogenous insulin, pancreatic β-cell failure progresses over time until most patients require insulin therapy.

Figure 2. Progression of Type 2 Diabetes



Exogenous insulin is needed when β-cell secretory capacity falls below the requirements for insulin to maintain good glycemic control, even in the presence of oral antidiabetic drugs (OADs).[16] In some patients with type 2 diabetes who may not tolerate OADs or in whom they may be ineffective, insulin must be initiated at the time of diagnosis. This approach is particularly important in patients who present with severe symptomatic hyperglycemia. It is worth remembering that 5% to 10% of individuals with new presentations of diabetes at any age have type 1 diabetes, which may be essentially impossible to distinguish initially. More generally, most patients will eventually require insulin therapy due to the progressive nature of type 2 diabetes that leads to insulin deficiency. The United Kingdom Prospective Diabetes Study (UKPDS) showed that over a 6-year follow-up period, approximately half the participants with new onset diabetes treated with sulfonylureas or metformin required the addition of insulin; the investigators predicted that most of the patients would need insulin during their lifetimes.[4]

Treatment Should Target the Underlying Pathophysiology

Therapy for diabetes should be correlated to the pathophysiology of the disease (ie, β-cell deficiency and insulin resistance) and mimic physiological (basal and prandial) secretion of insulin.[17] Exogenous insulin corrects the insulin deficiency; when dosed properly, it is the most effective medication for treating uncontrolled diabetes and has an excellent safety profile.[5,18] The potentially devastating consequences of uncontrolled diabetes underscore the need to treat with the most effective agents for maintaining glycemic control.

Treatment Goals Are Not Being Met

In the United States, quality of care for individuals with diabetes has improved over the last decade, but there is much room for improvement—key treatment goals are still not being met. Analysis of data from 2 large, federally funded surveys (the National Health and Nutrition Examination Survey [NHANES] and the Behavioral Risk Factor Surveillance System [BRFSS]) showed that the proportion of patients with diabetes having A1C levels <6% decreased from 23.4% to 16.4% over the last 10 years.[19] Only 42.3% of adults have A1C levels at the ADA goal of <7%, whereas 20.6% of patients have poor glycemic control (A1C >9%). The proportion of patients meeting the recommended level of low-density lipoprotein (LDL) cholesterol <100 mg/dL increased by 22% (from 42.4% to 64.2%) over the last decade, and increasing proportions of patients underwent an annual lipid profile (84.6%), eye examination (67.7%), and foot examination (68.3%). However, there was no improvement in the proportion of patients meeting their criteria of controlled hypertension (<140/90 mm Hg), which remained at ~68%. In conclusion, 1 in 5 patients with diabetes currently has extremely poor glycemic control (A1C >9%); 2 in 5 patients have poor LDL cholesterol control (LDL cholesterol ≥100 mg/dL); 1 in 3 has poor hypertension control (≥140/90 mm Hg); and 1 in 3 has not received annual eye or foot examinations.[19] These data suggest that more aggressive management of diabetes is warranted, including modification of treatment regimens when patients fail to meet glycemic, and other, targets.

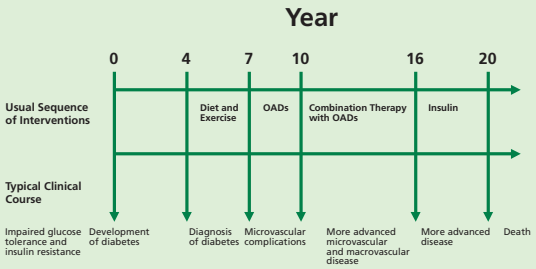
Current Stepwise Approach Is Not Working

The traditional approach to the management of type 2 diabetes has been stepwise, beginning with lifestyle modification (diet and exercise), followed by antihyperglycemic monotherapy (usually OADs), combination OAD therapy, and, finally, insulin therapy, either in combination with an OAD or alone (Figure 3). Recently, the incretin or glucagon-like peptide-1 analog (exenatide, Byetta®) and amylin analog (pramlintide, Symlin®) have become available, and their place and

timing in the treatment of type 2 diabetes has yet to be established. Transition from one medication to another was often protracted, with long periods of inadequate control before treatment was modified. Success of the stepwise approach depends on aggressive monitoring and changing the therapy when the targeted goals are not met.

Given that less than half of patients with diabetes currently meet the ADA recommended glycemic goal of A1C <7%, the stepwise approach as currently implemented is not working.

Figure 3. Stepwise Approach for Treatment of Type 2 Diabetes



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When used as monotherapy or when added as a second or third agent, an OAD can lower A1C levels by 0.5% to 2.0%.[20,21] One can expect a decrease in A1C of 0.5% to 1.0% when the incretin exenatide is added to OAD therapy.[22] In contrast, insulin can lower A1C to a desired target; its main limitation is the potential to cause hypoglycemia, which can usually be managed by careful monitoring of BG and adjustments of insulin doses or the lifestyle plan (monitoring, meals, and activity). Patients should be referred to self-management training programs to: 1) learn the knowledge and skills to manage their diabetes effectively, 2) identify barriers, 3) facilitate problem solving, and 4) develop coping skills to achieve effective self-care behaviors. Depending on the nature of the glucose excursions and severity of disease, insulin can be used in combination with OADs or alone.

Goal Is to Limit Diabetes-Related Complications

Several landmark trials have established that maintaining glycemic control with intensive insulin therapy reduces the risk of diabetes-related microvascular complications such as neuropathy, retinopathy, and nephropathy, and this benefit appears to persist for at least 4 years after intensive treatment ends.[23–25] In addition, 1 study found that intensive diabetes therapy for 6 years in patients with type 1 diabetes reduces the risk of any cardiovascular disease event (macrovascular complication) during long-term (17-year) follow-up.[26] Many patients with type 2 diabetes will have some type of macrovascular or microvascular complication by the time diabetes is diagnosed.[27] Analyses of data from the UKPDS showed that the incidence of clinical complications among patients with type 2 diabetes was strongly correlated with glycemia.[28] Correspondingly, UKPDS showed that each 1% reduction in mean A1C correlated with a reduction in risk of 21% for any end point related to diabetes, including death.[28] Based on these landmark trial findings, both the ADA[10] and the American Association of Clinical Endocrinologists (AACE)[29] have set aggressive targets for control of BG. The ADA recommends an A1C target of <6.0% in individuals to the extent that it can be achieved without adverse effects such as hypoglycemia, with a population goal of <7.0%. The AACE goal is A1C ≤6.5%.

Development of Insulin Analogs and Premixed Insulin Analogs

Over the last decade, the greatest change and one of the most important advances in diabetes therapy has been the development of insulin analogs.[6] These analogs were developed to more closely mimic physiologic insulin secretion in their onset and duration of action compared with human insulin formulations. The availability of insulin analogs has simplified insulin dosing and adjustment, and increased flexibility for patients. As shown in Table 1, several formulations of insulin analogs and premixed insulin analogs are available. Insulin aspart, insulin glulisine, and insulin lispro are rapid-acting analogs that are administered just prior to meals, whereas insulin detemir and insulin glargine are long-acting analogs used for basal control (Table 1).

Although not a rapid-acting insulin analog, inhaled human insulin also has a more rapid onset of action than subcutaneous regular human insulin.[30]

Premixed insulin analogs provide both basal and prandial coverage in 1 injection; they are suitable for starting insulin therapy in patients who desire a simple and convenient regimen or in patients who are not willing to administer multiple daily injections (MDIs). Three products are currently available: (1) biphasic insulin aspart 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart); (2) biphasic insulin lispro 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro); and (3) biphasic insulin lispro 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro). The rapid-acting components of premixed analogs are more quickly absorbed and provide better postprandial coverage compared with human insulin premixed formulations.[9] Because of their more physiological time-action profiles, insulin analogs and premixed insulin analogs also lower the risk for

Table 1. Time-Action Profiles of Insulin Analogs and Premixed Insulin Analogs Currently Available in the United States

Formulation	Time to Onset of Action (hr)	Time of Peak Action (hr)	Duration of Action (hr)
Rapid-Acting Analogs			
Insulin aspart (NovoLog®)	<0.5[31]	1-3[32]	3-5[32]
Insulin glulisine (Apidra®)	NA	~1[33]	~3.5[33]*
Insulin lispro (Humalog®)	0.25-0.5[34]	0.8-4.3[35]	4-6[34]
Long-Acting Analogs			
Insulin detemir (Levemir®)	0.8-2.0[36]	3.2-9.3[36]	5.7-23.2[37]
Insulin glargine (Lantus®)	1[38]	No consistent peak[38]	10.8-24[38]
Premixed Insulin Analogs			
Biphasic insulin aspart 70/30 (NovoLog® Mix 70/30)	<0.5[39]	1-4[39]	≤24[39]
Biphasic insulin lispro 75/25 (Humalog® Mix75/25™)	<0.5[40]	1-6.5[40]	~22[40]
Biphasic insulin lispro 50/50 (Humalog® Mix50/50™)	<0.5[41]	2.3[41]	~22[41]

Wide interindividual variation in time to onset of action, time to peak action, and duration of action can occur.
NA = not available; data presented graphically in Figure 3 of the Apidra package insert. *Calculated from data in Apidra package insert.

hypoglycemia, especially nocturnal hypoglycemia, compared with human insulin formulations.[7–9,42]

When to Initiate Insulin Therapy

Insulin should be prescribed when it is likely to be the most effective agent, rather than waiting until patients fail to reach normal A1C levels with lifestyle modifications and OADs. Insulin should be considered as initial therapy in patients with severe hyperglycemia (FPG >250 mg/dL), weight loss, ketonuria, and intolerance or contraindications to OADs.[43] It should also be considered in pregnancy, the perioperative period, and the inpatient setting. At present, many patients have had type 2 diabetes for 10 to 15 years and may have developed complications before insulin therapy was initiated.[44]

Since progressive β-cell decline and diminishing endogenous insulin secretion means that insulin is eventually required by the majority of patients with type 2 diabetes, some authorities advocate introducing insulin earlier in the treatment plan.[45,46] Poorly controlled patients have high morbidity and mortality rates, low quality of life, and incur higher healthcare costs.[45] Therefore, it is essential that glycemic control be maintained through treatment with the most effective regimens in a timely manner. Availability of insulin analogs and premixed insulin analogs, as well as development of more convenient delivery systems, has alleviated some barriers and fears associated with insulin use.[46]

Table 2. Common Concerns in Patients Starting Insulin Therapy[47]

Concern	Resolution
Initial anxiety	More education and support about the role of insulin in treating diabetes.
Feeling of personal "failure"	Inform patient that diabetes is a progressive disease and explain β-cell failure.
Hypoglycemia	Educate about the signs and symptoms as well as prevention and treatment.
Injection phobia	Teach self-injection with saline. Explain devices including those that conceal needle as well as availability of fine needles.
Weight gain	Explain improved metabolic control and efficiency. Adjust diet and physical activity. Carefully plan snacks and incorporate into meal plan.
Lifestyle factors	Explain flexible and multiple insulin regimens and devices that allow discreet dosing. Insulin administration can enhance lifestyle flexibility because dosing can be adjusted to accommodate activity and changes in meal plans.
Lack of support	Explain role of diabetes-care team and education for family and friends.
Myths about insulin	Explain treatment options and progressive nature of disease at initial diagnosis. Use evidence-based literature to dispel myths.
Preventing complications	Explain how insulin can reduce the risk of further microvascular and, perhaps, macrovascular complications.

Addressing Patient Concerns

Despite uncontrolled hyperglycemia and increasing A1C, patients may resist starting insulin for a variety of reasons (Table 2).[47] The healthcare provider can help patients make informed decisions by understanding patient concerns and providing appropriate responses. Table 2 shows common concerns and strategies that can help patients overcome these issues. Patients should also be referred to a diabetes team to learn appropriate self-management skills.

Which Insulin Formulation?

The aim of initiating insulin therapy is to achieve optimal glycemic control without causing hypoglycemia or excessive weight gain. In choosing an insulin formulation, clinicians typically consider its onset, peak, and duration of action; equally important are the needs, concerns, and capabilities of the patient. While a basal-bolus regimen—including a long-acting insulin analog once or twice a day and rapid-acting insulin analogs at each meal—is ideal in terms of physiological action and overall glycemic control, many patients are reluctant to initiate insulin with a regimen requiring MDIs.[48] However, they may be willing to start using a less intensive regimen, and transition to MDI later if necessary. It is important that the regimen chosen match the needs and capacities of the individual patient.

Studies have investigated the use of basal insulin or premixed insulin analogs for patients with type 2 diabetes poorly controlled on OADs. Riddle and coworkers[49] showed that among 756 overweight patients treated with OADs with A1C between 7.5% and 10.0%, adding bedtime basal insulin (either glargine or neutral protamine Hagedorn [NPH], once daily) to existing OAD therapy safely achieved A1C levels ≤7.0% for 60% of the patients.[49] Although the efficacy and weight gain with both regimens was similar, the incidence of hypoglycemia, particularly at night, was moderately lower with insulin glargine. A related study showed that more patients treated with insulin detemir reached an A1C <7% without hypoglycemia compared with NPH; there was also less weight gain with insulin detemir.[50] Thus, long-term basal analogs have similar efficacy but with less risk of hypoglycemia compared with NPH insulin.

When once-daily glargine was compared with twice-daily biphasic insulin aspart 70/30 in patients receiving OADs with A1C ≥8.0%, the A1C reduction was significantly greater in the biphasic insulin aspart group, especially for the subset of patients with baseline A1C >8.5%, but with an increased risk of minor hypoglycemia.[51] Similarly, Malone and colleagues[52] showed that twice-daily premixed insulin lispro 75/25 resulted in lower A1C levels than once-daily glargine when one or the other insulin regimen was added to existing metformin therapy. Thus, patients with type 2 diabetes poorly controlled on OADs benefit from the addition of insulin to existing oral therapy: the addition of either once-daily basal insulin or twice-daily premixed insulin confer benefit, but the latter appears to achieve better overall glycemic control. In practice, clinicians may start patients on a once-daily evening injection of premixed insulin, and add the second (morning) injection as needed.[53]

The following case study provides an example of a patient not achieving adequate glycemic control on OADs, and consequently initiating insulin therapy.

Case 1: Patient was not maintaining glycemic control on combination OAD therapy and premixed insulin analog therapy was initiated.

WD is 59 years old. She was diagnosed with type 2 diabetes 10 years ago. Her body mass index (BMI) is currently 25 kg/m^2 with a weight of 168 pounds and height of 5'9". WD works full time and commutes 40 to 60 minutes per day depending on traffic. WD works in the Sales Department and her mealtimes are not set. WD has also stated that she has no time for exercise and that she is really too tired to even consider it.

WD was initially treated with metformin 500 mg BID and then a secretagogue was added. Two years ago, a thiazolidinedione (TZD) was started. With each additional OAD, WD had a 0.5% to 1% reduction in her A1C values. Her most recent OAD regimen included maximal doses of metformin, the secretagogue, and the TZD.

At a regular visit several months ago, WD complained of nocturia, polyuria, and polyphagia. WD's fasting BG (FBG) level was 180 mg/dL and postprandial values were frequently >250 mg/dL. Her A1C value was 8.2%.

Take-Home Points

This patient is now at the final phase of the conventional stepwise approach (Figure 3). Control is inadequate on combination OAD therapy. The monthly cost of her treatment regimen is ~$450 for diabetes pills alone. Both FBG and PPG are high, and the A1C of 8.2% suggests that both postprandial and fasting glucose excursions are contributing to the overall hyperglycemia.[12] Meals are inconsistent in both timing and content. What treatment options could be recommended for this patient who was reluctant to commence insulin therapy?

Options for initiating insulin therapy

Plan A – Prescribe premixed analog at dinnertime (eg, biphasic insulin aspart 70/30 or biphasic insulin lispro 75/25) with the option to add a second injection if needed. Retain metformin and TZD. Use of a secretagogue based on PPG values at breakfast and lunchtime; discontinued at dinnertime. Later, it may be possible to reduce or eliminate the doses of oral agents once control is achieved.

Pros
- Provides both prandial and overnight basal insulin coverage with single injection
- Insulin can be administered by syringe, pen, or insulin doser 0 to 15 minutes before dinner
- Premixed analog eliminates mixing errors

Cons
- Fixed ratio of rapid- and intermediate-acting analogs precludes the independent adjustment of the basal and prandial components
- Requires a fixed meal size and may require a bedtime snack to prevent nocturnal hypoglycemia

Plan B – Prescribe a long-acting insulin analog (eg, insulin detemir or insulin glargine) with the option to add a rapid-acting insulin analog if PPG is not controlled. Retain all OADs, especially secretagogues, to help with endogenous insulin release with meals. Doses may be reduced once control is achieved.

Pros
- Provides basal insulin coverage for up to 24 hours with a single injection
- Reduces the risk of hypoglycemia related to eating less than planned
- Rapid-acting component can be administered by syringe or insulin pen 0 to 15 minutes before meal

Cons
- Insulin detemir or insulin glargine cannot be mixed with other insulin preparations
- Does not remedy the postmeal excursions; although they may improve with reduced premeal glucose

Plan C – Prescribe mealtime rapid-acting insulin analog (eg, insulin aspart, insulin glulisine, or insulin lispro) with the option to add a long-acting insulin analog if FPG is not controlled. Retain all OADs. May consider initiating a long-acting sulfonylurea in the evening to help with fasting glucose.

Pros
- Insulin can be administered using a syringe or pen 0 to 15 minutes prior to the meal
- Lowering the postmeal readings may lower the FBG moderately and will impact the A1C
- Allows WD to decide when she wants to eat and to alter the insulin dose based on the food she plans to eat

Cons
- Requires a dose of insulin before each meal; could be initiated at any meal with 1 or more servings (15 grams) of carbohydrates
- Does not provide basal coverage, although fasting and premeal glucoses may be adequately managed based on action of oral agents

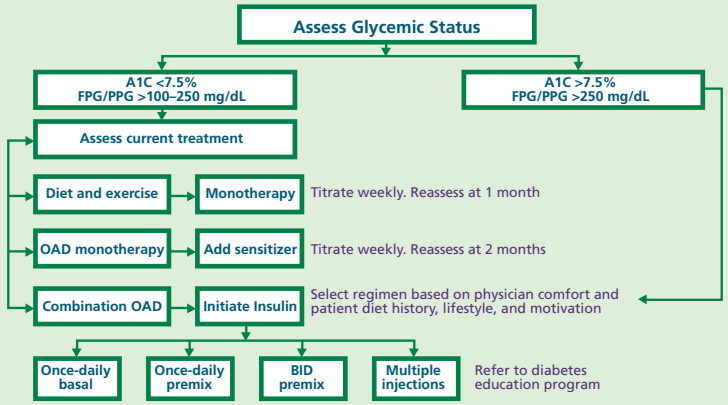
Note that other options for this patient could include the use of non-analog insulin, inhaled insulin, and exenatide.

The patient and the healthcare provider decided to try Plan A because it is a simple regimen that has the potential to control both the postprandial and basal glucose excursions in 1 injection. WD decided to administer 1 injection of a premixed insulin analog just prior to dinner, her largest meal. The diabetes educator helped WD with dinner choices to ensure a consistent carbohydrate intake and identified a realistic plan to increase physical activity. After 3 months on Plan A, WD's FPG had decreased to 110 mg/dL and her PPG readings were usually <140 mg/dL. Her A1C had decreased to 7.2%. WD was asked to check her BG levels 2 hours after breakfast and lunch to determine if her postprandial BG was in the target range. WD reported that she has reduced her portions of food, has more energy, and is now walking 30 minutes 3 times a week. WD was also counseled that she may have to use 2 injections of the premixed analog to lower A1C further.

Initiating and Titrating Insulin Therapy

As illustrated in Case 1, patients may be started on an insulin regimen if they do not achieve adequate glycemic control on combination OADs. Figure 4 depicts a recently published algorithm suggesting when and how to initiate insulin therapy in a primary care practice.[48]

Figure 4. Algorithm for Initiating Insulin Therapy (Hirsch et al. Protocol)



Titrate weekly for 1 month or until glycemic targets achieved. Monitor monthly and adjust as needed. Transition to different regimen in 3-6 months if needed for glycemic targets or if hypoglycemia is a problem. Adapted from Hirsch IB et al. *Clin Diabetes*. 2005;23:78–86.

As shown in Figure 4, patients with very high BG (eg, FPG >250 mg/dL) should be started on insulin immediately. Treatment with OADs is a reasonable approach for patients with less severe hyperglycemia. Within 3 months, if glycemic targets are not achieved, insulin should be initiated. While the patient in Case 1 started insulin on a once-daily premix regimen, other regimens were also considered and are depicted in Figure 4. Patients starting insulin often remain on their OADs, which may be gradually reduced in dose or eliminated.

Table 3. American Diabetes Association Recommendations—Adding Insulin to Oral Antidiabetic Drug Therapy

Fasting Levels Above Target	Fasting Levels at Target; Values During Day Above Target
• Single bedtime injection of detemir, glargine, or NPH	• Add either regular or rapid-acting insulin before meals
• Starting dose 0.15 unit/kg; titrate up in 2-unit increments every 5–7 days based on fasting blood glucose	– Dose = 1 unit/10 grams carbohydrates in the meal
• Monitor blood glucose before breakfast and supper	• Add either detemir, glargine, NPH, or premixed insulin analog injection before breakfast
	– Start 0.1 unit/kg, titrate based on blood glucose monitoring results
	– If already treated with evening insulin, reduce evening insulin simultaneously by similar amount and titrate

NPH = neutral protamine Hagedorn

Adapted from American Diabetes Association. *Practical Insulin: A Handbook for Prescribers*. Alexandria, Va: American Diabetes Association; 2002.

In choosing the starting dose of insulin, many clinicians empirically begin with a low dose. In general, 10 units per injection is considered a safe starting dose for once- and twice-daily regimens.[48] Beginning at a low dose and slowly titrating to higher doses helps avoid hypoglycemia and builds patient confidence.

The starting dose of insulin may also be calculated based on weight, and a common starting dose is 0.15 unit/kg body weight/day, but most patients will need higher doses to achieve glycemic targets.[48] Overweight patients require higher doses because of greater insulin resistance. Table 3 depicts an algorithm for adding insulin to OAD therapy that incorporates weight-based insulin dosing. Another treatment algorithm that suggests how to initiate insulin for type 2 diabetes, developed by the American College of Endocrinology, may be found at http://www.aace.com/meetings/consensus/odimplementation.

Once insulin has been initiated, the dose must be titrated every few days or weekly according to results from the patient's BG records.

Blood Glucose Monitoring

BG monitoring is essential for titration and evaluation of the insulin regimen. A reasonable plan involves varying among fasting, premeal, postprandial, bedtime, and mid-sleep levels, aiming to get at least 1 reading at each time of day over a week; this requires records to keep track of the values. Another common technique is to have patients monitor fasting and 1 postprandial BG value and record each result. The frequency of monitoring will depend on the insulin regimen, the severity of hyperglycemia, the magnitude of glucose excursions, patient willingness, insurance coverage of test strips, and whether there is a history of hypoglycemic unawareness. Those using the most injections generally need to monitor more frequently to optimize the treatment program; patients on MDI may need to check the BG before each meal and at bedtime each day with frequent additional postprandial checks to help with titration of the rapid-acting component. BG levels should be checked if the individual has signs or symptoms of hypoglycemia. Patterns of highs or lows indicate that a dose adjustment may be needed. No clear patterns of BG readings often indicate the need for greater attention to lifestyle issues and adherence with treatments.

To titrate the insulin dose, the patient may call or fax BG readings to the healthcare provider, and dose changes can be given to the patient over the phone. Alternatively, the patient may self-titrate and report both monitoring and adjustment data to the healthcare provider on a weekly basis.

BG should be measured once or twice daily (prebreakfast and/or presupper) depending on the regimen. With a twice-daily regimen, the prebreakfast insulin dose should be adjusted based on the recorded presupper BG levels over the previous 3 to 7 days. The presupper insulin dose should be adjusted based on the recorded prebreakfast BG levels over the previous 3 to 7 days. The suggested titration schedule appears in Table 4.[48] The insulin dose should not be increased if hypoglycemia (BG <70 mg/dL) or symptoms of hypoglycemia are present.

Table 4. Suggested Titration Schedule for Once- or Twice-Daily Insulin Regimens

Average BG Last 3–7 days (mg/dL)	Dosage Change (units/day)*
<80	–2
80–109	No change
110–139	+2
140–179	+4
>180	+6

*Do not increase dose if hypoglycemia (<70 mg/dL) or symptoms are present.

Titration should occur weekly for the first month or until glycemic targets are achieved. If patients are not meeting targets after 3 to 6 months, or if recurrent hypoglycemia limits titration, the regimen may need to be changed.

The following case studies present examples of initiation and adjustment of insulin therapy using different regimens.

Initial Coverage with a Long-Acting Insulin Analog

While the patient in Case 1 began insulin therapy using a premixed formulation, another common way to begin is to add a long-acting insulin analog at bedtime to OAD therapy. Problems of nocturnal hypoglycemia with NPH insulin may be overcome by using a long-acting insulin analog such as insulin detemir or insulin glargine, because the pharmacokinetic profiles of long-acting insulin analogs are relatively peakless compared with NPH insulin.[49,54]

Case 2: Patient with elevated A1C and neuropathy on high doses of OADs was successfully treated with a long-acting insulin analog formulation.

PM is a 53-year-old male with a 3-year history of type 2 diabetes. His BMI is 30 kg/m^2. His A1C value is 8% on near maximum doses of OADs, which include metformin, a sulfonylurea, and a TZD. PM is very concerned because a recent eye exam showed early retinopathy. Because he travels frequently for work, mealtimes, exercise, and BG monitoring are erratic. A review of his meter's memory revealed that he had checked his BG levels only 7 times in the past month. PM is now willing to do whatever it takes to get his BG levels under control. After explaining the therapeutic options, his medications were changed to a long-acting insulin analog at night and OADs during the day. He was started on 10 units of a long-acting insulin analog at bedtime, and the dose was titrated to 25 units at bedtime. He also met with a registered dietitian to design a meal and exercise plan that he could fit into his lifestyle.

After 1 month of this new regimen (metformin, a TZD, and 25 units of a long-acting insulin analog at bedtime), the patient's average BG levels were an FPG of 120 mg/dL and PPG <180 mg/dL. After 3 months of this regimen, the patient's A1C was 6.8%. The patient will need to continue monitoring his BG levels because over time he may eventually need a rapid-acting insulin analog to keep his PPG under control.

Take-Home Points

In patients with erratic schedules or unpredictable activity, a long-acting insulin analog may be less likely to result in hypoglycemia than an intermediate-acting insulin such as NPH. Because individual dose requirements can vary considerably depending on the degree of endogenous insulin deficiency, dosing should be based on treatment goals and titration. Since basal insulin regimens do not cover the PPG excursions, PM's OADs were retained. However, if the OAD therapy does not provide optimal PPG control, he may eventually require a rapid-acting insulin analog after each meal or a twice-daily premixed insulin analog.

Another example of initiating insulin therapy using a once-daily, long-acting formulation follows. In this case, the importance of prandial control is highlighted.

Case 3: Patient was successfully treated with a long-acting insulin analog formulation but required an OAD for prandial control.

LP is an obese (BMI, 46 kg/m^2) 56-year-old woman who presented with a 6-year history of type 2 diabetes and insulin resistance. Her FPG (161 mg/dL) and A1C (9.6%) levels at presentation were both elevated. She was taking a combination of a sulfonylurea and metformin as well as medication for hypercholesterolemia and hypertension. To address her elevated FPG, a long-acting insulin analog was prescribed at bedtime and the sulfonylurea was discontinued. Her meal plan was also modified to reduce portions and improve variety. After 2 weeks, her FPG levels were consistently <130 mg/dL. One month later at her diabetes education class, LP's postprandial BG was measured after she drank a regular soft drink. The reading of 327 mg/dL shocked her as she was accustomed to fasting readings <130 mg/dL. LP learned more about food choices and portions and began PPG monitoring. Even when her food choices were within her meal plan, her postprandial readings were out of range and a secretagogue was initiated at breakfast and dinner. After 3 months, her FPG range was 115 to 125 mg/dL, PPG range was 185 to 205 mg/dL, and A1C was 7.2%.

Take-Home Points

A bedtime long-acting insulin analog for this insulin-resistant patient combined with diabetes self-management education was an appropriate introduction to insulin therapy. However, this case also illustrates the importance of PPG monitoring. Patients often need to see elevated postprandial readings before they will make further changes in their therapy. Even with careful adherence to her meal plan, treatment of postprandial hyperglycemia was necessary to control PPG in this case. The patient preferred to start with a prandial secretagogue rather than administer additional injections of insulin. In retrospect, therapy with the secretagogue may not have been necessary if the sulfonylurea was not discontinued when insulin therapy was initiated.

Coverage of FPG and PPG with a Premixed Insulin Analog

Premixed insulin analogs enable both PPG and FPG to be covered with the same injection. A premixed formulation can be administered once or twice daily, sometimes in conjunction with OAD therapy.

Table 5. Glucose Levels in Patient From Case 4

Day	Before Breakfast (mg/dL)	Before Lunch (mg/dL)	Before Dinner (mg/dL)	Bedtime (mg/dL)
Sunday	146	147	166	193
Monday	*	*	115	*
Tuesday	150	129	*	98
Wednesday	130	70	*	129

*Blood glucose checks not performed.

Case 4: Patient was successfully treated with a premixed insulin analog formulation and both PPG and FPG were monitored.

TR, a 57-year-old woman with a BMI of 33.2 kg/m^2, was diagnosed with type 2 diabetes 9 years ago. She was referred to an endocrinologist for management of uncontrolled hyperglycemia and diabetes-related complications including retinopathy. TR described several weeks of increased polyuria and polydipsia. Random BG levels measured at home were in the 347 to 514 mg/dL range. Her physical activity was limited by comorbid osteoarthritis. She had recently seen a registered dietitian and was trying to follow her dietary recommendations. At presentation, TR's medications included an angiotensin-converting enzyme (ACE) inhibitor and a sulfonylurea. Previous experience of gastrointestinal side effects of metformin precluded its use. Her A1C at this visit was 11.5% (goal <6.5%–7.0%), whereas the last available measurement 1 year ago was 7.8%. Serum chemistry tests revealed normal renal and liver function.

TR was started on a premixed insulin analog formulation beginning with 10 units, 15 minutes before breakfast, and 10 units, 15 minutes before dinner. This premixed insulin analog formulation contains an intermediate-acting insulin protamine suspension which provides basal coverage and a rapid-acting insulin analog which provides prandial coverage. Her sulfonylurea was discontinued, and she self-titrated her insulin to 20 units in the morning and 22 units in the evening based on BG monitoring results. She returned to the office a few weeks later with the decreased BG levels reported in Table 5.

Six months later, her A1C value was 7.4%.

Take-Home Points

This patient with long-standing type 2 diabetes with microvascular complications presented with severe, symptomatic hyperglycemia. Due to the severity of her BG elevation, her physician prescribed a twice-daily regimen of a premixed insulin analog. The initial low dose was selected to avoid hypoglycemia and was titrated up.

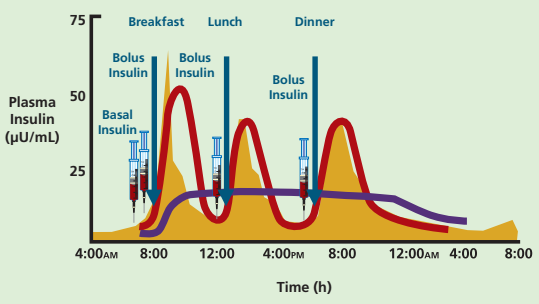
In retrospect, earlier initiation of insulin therapy in this patient may have prevented or delayed the diabetes-related complications. Additional dose titration will be necessary to reduce A1C further. The patient will also need follow-up with a registered dietitian to establish consistent mealtimes and carbohydrate content of meals, and she should be instructed not to skip meals as the prandial component of her insulin regimen may cause hypoglycemia.

Basal-Bolus (Multiple Daily Injection) Therapy

Basal-bolus therapy aims to mimic basal and postprandial insulin secretion. These regimens may be used to achieve physiological BG control in patients with advanced β-cell deficiency and complications. They can also be used when the patient requires more flexibility than offered by other regimens. Successful use of intensive basal-bolus therapy requires comprehensive patient education, including carbohydrate counting, insulin-to-carbohydrate ratio, and using a correction factor for insulin dose adjustment. Carbohydrate counting is discussed in more detail below.

An MDI regimen often includes a rapid-acting insulin analog before each meal and a long-acting insulin analog once a day (Figure 5). Patients can coordinate the timing of injections with meals, giving them more flexibility with mealtimes and lifestyle. Patients should monitor their BG levels frequently (fasting, before most meals, occasional postprandial, and bedtime) and determine the impact of carbohydrate content of meals on the dose of insulin required. An insulin pump can be used in place of MDI in patients who are suitable candidates for continuous subcutaneous insulin infusion therapy.

Figure 5. A Representation of Rapid-Acting and Long-Acting Insulin Analog Time-Action Curves



Carbohydrate Counting and Adjustment of Mealtime Insulin Doses

Carbohydrate counting is a skill that requires the patient to have good math skills and the ability to problem solve to determine the carbohydrate content of food eaten. Patients on MDI can adjust the mealtime insulin dose based on the estimated carbohydrate content of the meal and the BG reading.[55] For example, 1 unit of a rapid-acting analog can be given for every 10 to 15 grams of carbohydrates consumed.[56] Subsequently, the insulin-to-carbohydrate ratio can be titrated to optimize control of PPG and the glucose before the next meal.

An obese individual will commonly need a ratio of 1:5 (1 unit of a rapid-acting insulin analog for every 5 grams of carbohydrates to be consumed) and sometimes may need as much as 1 unit per gram of carbohydrate. A thin, insulin-sensitive individual may require a ratio of as little as 1:20. During titration, BG should be checked 1 to 2 hours after the meal to determine if the dose is correct. Postprandial BG should be within 30 to 40 points of the preprandial value when the insulin-to-carbohydrate ratio is optimal.

If the premeal glucose is high, more (supplemental) insulin may be given in addition to the normal prandial insulin dose. The extra insulin will vary according to a patient's sensitivity to insulin. Patients may require an additional 1 to 2 units for every 50 mg/dL the premeal glucose level is above the target.[55] Alternatively, it is often possible to estimate how much 1 unit of a rapid-acting insulin analog will decrease the plasma glucose over 3 hours, using the formula 1500/body weight in kilograms.

An example is as follows: Patient ND uses an insulin-to-carbohydrate ratio of 1:15 and has been prescribed a dose of 1 unit of insulin for every 50 mg/dL that the blood sugar before meals is >100 mg/dL. He is about to eat dinner which he estimates contains 90 grams of carbohydrates. Although his premeal BG target is 100 mg/dL, the actual reading was 200 mg/dL. Therefore, he may have underestimated the carbohydrate content at the previous meal resulting in a high predinner reading, or his basal insulin dose may be inadequate. ND will take 6 units of a short-acting insulin analog to cover the 90 grams of carbohydrates plus another 2 units of a short-acting insulin analog to correct for being 100 mg/dL over his target glucose. His total insulin dose with dinner will be 8 units.

Case 5: Patient with elevated A1C despite aggressive OAD therapy reluctantly started basal insulin and ultimately required MDI to achieve optimal glycemic control.

EP is a 60-year-old woman with a BMI of 26.5 kg/m^2 (height, 5'5"; weight, 159 lb). She was diagnosed with type 2 diabetes 6 years ago. EP reported that her BG levels, checked at home upon waking and at bedtime, as well as after each meal, ranged from 200 to 350 mg/dL before and after meals, respectively. She had a regular exercise routine that included walking 4 to 5 times a week for 30 minutes and made healthy food choices. She described burning pains in both feet at night. Medications at presentation included a sulfonylurea and metformin 500 mg BID; she reported that higher doses of metformin had caused diarrhea. A TZD had been prescribed in the past, but was discontinued because of pedal edema. The A1C was 9.3%.

EP was reluctant to start insulin therapy but agreed to 1 injection of long-acting insulin analog, 10 units, once daily at bedtime. The dose was titrated based on BG monitoring results phoned in to the physician. At follow-up 3 weeks later, she reported administering 30 units of the long-acting insulin analog at bedtime and continuing OADs. FPGs were between 70 and 100 mg/dL, but PPGs were all >250 mg/dL. Her physician suggested supplementing with a rapid-acting insulin analog, starting with 1 injection of 5 units with her largest meal of the day, reducing the long-acting insulin analog by 5 units at the same time. She agreed and subsequently discovered that her BG excursions were better controlled if she administered the rapid-acting insulin analog with all of her meals. The sulfonylurea was discontinued.

EP met with a diabetes educator and learned how to use a pen device for delivering the rapid-acting insulin analog. She also learned how to estimate the carbohydrate content of her meals so that she may adjust the rapid-acting insulin analog dose, and discussed healthy meal choices and strategies to minimize weight gain. She carries her insulin pen at all times and is very pleased with her ability to manage her BG levels. After 3 months, FPGs averaged 113 mg/dL and PPGs averaged 153 mg/dL. Her A1C had decreased to 6.9%.

Take-Home Points

Patients who need multiple injections of insulin can begin with a once-daily injection of a long-acting insulin analog with the subsequent addition of a rapid-acting insulin analog at mealtimes. Working with a diabetes-care team and an easy-to-use insulin delivery system helped this patient transition to an MDI regimen. The improvements in glycemic control, flexibility, ownership, and general well-being have also helped this patient accept the regimen.

Case 6: Patient using a premixed human insulin formulation presented with hypoglycemia and was switched to a basal-bolus regimen.

RW is a 57-year-old African American male who was diagnosed with type 2 diabetes 12 years ago. He travels frequently for work and finds it difficult to eat meals on time and make dose adjustments for the carbohydrate content of his meals. RW's last A1C was 9.0%. He was injecting 60 units of premixed human insulin 70/30 before breakfast and an additional 30 units before dinner. RW presented to his physician with complaints of hypoglycemia in the afternoon. His insulin regimen was

changed to an MDI regimen with insulin analogs to allow more flexibility.

The physician started the patient on 30 units of a long-acting insulin analog at bedtime and followed the registered dietitian's recommendation to initially use 1 unit of a rapid-acting insulin analog for every 15 grams of carbohydrates eaten at each meal. After 3 weeks, his average BG values were as shown in Table 6. To determine if the insulin-to-carbohydrate ratio is correct, RW was advised that the 2-hour PPG should be within 30 to 40 mg/dL of the premeal value.

Table 6. Glucose Levels in Patient From Case 6

Blood Glucose Checks	Values (mg/dL)
Fasting blood glucose	123
2 hrs after breakfast	155
Before lunch	*
2 hrs after lunch	*
Before dinner	115
2 hrs after dinner	169

*Blood glucose not tested.

RW was concerned because his 2-hour PPG values were still greater than his target goal of 140 mg/dL. He contacted his primary care physician and registered dietitian and they recommended 1 unit of rapid-acting analog for every 12 grams of carbohydrates. A week later, on a return visit to the physician, the insulin-to-carbohydrate ratio was increased to 1:10 and finally to 1:8 two weeks later. It was also recommended that he keep a food diary and compare BG levels after meals so the optimal insulin-to-carbohydrate ratio could be determined.

The patient followed these recommendations and met his fasting, premeal, and postprandial BG goals. After 3 months, his A1C had been reduced to 7.2%, although he had gained 3 pounds. The patient agreed to walk for 20 minutes after supper each night and to cut back on his serving size and frequency of ice milk after supper. The more rapid action and duration of activity of the rapid-acting analog formulation may have helped resolve his problems with hypoglycemia.

Take-Home Points

Patients with irregular mealtimes and schedules often need to use flexible insulin dosing with an MDI regimen to achieve optimal glycemic control. Furthermore, it is important that the prandial doses are adjusted by calculating the carbohydrate content of the meal and by monitoring PPG. Further adjustments will be necessary to get A1C between 6.5% to 7.0%.

Case 7: Patient using premixed insulin analog improved glycemic control after switching to an MDI regimen.

DS is a 65-year-old recently retired businessman who was diagnosed with type 2 diabetes 10 years ago. For the last 2 years he has been injecting insulin. He has a history of hypertension and hyperlipidemia which are well controlled. At the last ophthalmology visit, he was found to have pre-proliferative retinopathy.

DS is using a premixed insulin analog. He takes 47 units in the morning with breakfast and 35 units with his evening meal. His wife comes with him to every clinic visit and prepares most of his meals and snacks. He follows a meal plan with consistent carbohydrate content except on the days when he plays golf with his friends.

His BG levels over the past week were as shown in Table 7.

On Monday, DS played golf and had a larger than usual lunch with his friends. He took extra units of the premixed insulin analog to cover his high predinner glucose but awoke in the middle of the night with

Table 7. Glucose Levels in Patient from Case 7

Day	Before Breakfast (mg/dL)	Before Lunch (mg/dL)	Before Dinner (mg/dL)	Bedtime (mg/dL)	3:00 AM (mg/dL)
Friday	180	60	215	150	*
Saturday	125	85	191	*	*
Sunday	203	*	225	*	*
Monday	162	*	348	*	47
Tuesday	226	92	185	*	*
Wednesday	170	*	*	82	*
Thursday	123	*	*	*	*

*Blood glucose checks not performed.

symptoms of hypoglycemia, for which he ate a snack with some juice. His A1C at a recent visit was 7.9%.

DS and his physician agreed he needed to intensify his insulin therapy to prevent progression of diabetes-related complications. He has trouble with hyperglycemia following lunch and has occasional hypoglycemia at other times. He would also like to play golf more often if it would not worsen his glycemic control.

His physician started him on a basal-bolus MDI regimen. His current total insulin dose was 82 units/day. The physician prescribed 40 units of a long-acting insulin analog every evening and 10 to 15 units of a rapid-acting insulin analog with each meal. This provided about half of his total insulin dose as basal insulin and the other half as prandial insulin, which could be adjusted according to the carbohydrate content of each meal after he and his wife learned carbohydrate-counting skills.

Take-Home Points

In patients with type 2 diabetes and advanced β-cell dysfunction, an MDI insulin regimen provides the most physiologic insulin replacement. With an MDI basal-bolus regimen, near-normal glycemia can be achieved with less hypoglycemia. Most patients benefit from using a rapid-acting analog with each meal and the ability to vary the timing and the dose to account for changes in schedules and size of meals. Various easy-to-use insulin delivery systems can be used to administer the rapid-acting insulin analog in a convenient and discreet manner.

Additional Considerations When Initiating Insulin Therapy

Frequency of Blood Glucose Monitoring—Additional Factors

As described previously, frequency of BG monitoring depends on a number of factors, including insurance coverage of test strips. It should be noted that Medicare covers 1 strip per day for patients who are diet-controlled and/or on oral medications, and 3 strips per day for patients on insulin. In certain situations, Medicare will allow for increased testing (eg, BG fluctuating, dose adjustments, hyperglycemia/hypoglycemia present).

Dose Adjustments for Special Circumstances

Dose adjustments may be required if the patient takes medications that affect carbohydrate metabolism or responses to insulin such as steroids. Liver or renal disease can also affect the pharmacokinetics of insulin. Exercise, illness, stress, aberrant eating patterns, alcohol, and travel may also necessitate dose adjustments.

Using a Diabetes-Care Team Approach

Because diabetes is a multifaceted disease, a multidisciplinary team approach to disease management is recommended. In primary care practice, however, where the majority of patients are treated, the physician may lack the time and resources to educate patients. Collaboration with diabetes educators and other healthcare professionals should be part of the standard of care for patients with diabetes. A certified diabetes educator may be located by calling 1-800-TEAM-UP4 (832-6874). The hotline is staffed by a live operator who will search for an educator in a given area based on zip code. Other resources for the diabetes team and patient are available from the following Web sites:

- American Association of Clinical Endocrinologists at *http://www.aace.com/pub/pf/index.php*
- American Association of Diabetes Educators at *http://aadenet.org/GeneralDiabetesInfo/index.html*
- American Diabetes Association at *http://www.diabetes.org*

The patient should be intimately involved in all aspects of care including the choice of therapy. Many concerns about insulin therapy are manageable and can be prevented by careful monitoring and dose adjustments.

Healthcare professionals working with patients with diabetes are more than just teachers and providers; these individuals are expert coaches who lead the patient through the complexities of insulin therapy and help them learn problem-solving skills. Apart from insulin administration skills and delivery options, patients also need to learn the 7 behaviors that are paramount in diabetes self-management—healthy eating, being active, monitoring, taking medications, problem solving, healthy coping, and decreasing risks. The skills involved in making adjustments for exercise, travel, sickness, and stress levels are part of a diabetes self-management curriculum.

Weight gain with insulin can occur because of improved glycemic control, less glucosuria, or overinsulinization, not necessarily because insulin is anabolic. Furthermore, snacking to prevent hypoglycemia or feed the peaks of human insulin can add unnecessary calories. Patients can work with registered dietitians to minimize any weight gain due to more efficient metabolism or snacking. In addition, with insulin analogs, snacking is not always required.

Improvements in Insulin Delivery Systems

Delivery of insulin by vial and syringe has been a considerable barrier to patient acceptance and adherence with insulin therapy.[57] Patients who were once limited to the single option of vial and syringe delivery now have the choice of using reusable (durable) or prefilled

(disposable) insulin pens, insulin jet injectors, insulin dosers, inhaled insulin, or an external insulin pump. The ideal insulin delivery system is one that provides accurate dosing while being comfortable and convenient for the patient. Other considerations for choosing the ideal delivery system include patient safety, social acceptability, affordability, and environmental issues. The fear of pain and other concerns with injections have been diminished by the availability of finer and smaller needles, and utilization of insulin pens and dosers. Development of insulin pumps that are no larger than a pager enables doses of insulin to be delivered as needed (basal-bolus) without the need for multiple injections. Other recent advances include real-time glucose sensors, which measure glucose levels every 5 minutes, with the results sent via a transmitter to an insulin pump. This enables sensor-augmented pump therapy in which patients may make immediate therapy adjustments based on continuous BG readings.[58]

Summary and Recommendations

- Because β-cell deficiency is an inevitable consequence of type 2 diabetes, insulin therapy should be initiated when patients are not able to meet glycemic goals with OADs.
- Currently in the United States, key treatment goals are not being met: less than half of patients with diabetes meet the ADA-recommended glycemic population target A1C of <7%.
- Since basal and PPG excursions both contribute to overall glycemic control, both FPG and PPG should be targeted if patients are to meet goals. While FPG is routinely monitored, PPG should be monitored mainly during titration of the insulin dose, and is most important for patients on basal-bolus (MDI) therapy.
- Goals for glycemic control and insulin doses should be individualized. Although various algorithms for calculating insulin dosage can be used as guidelines, most clinicians start with a low dose based on body weight and titrate up based on BG readings and meal carbohydrate content until goals are achieved.
- The insulin regimen should achieve glycemic control and minimize risk of hypoglycemia and other metabolic disturbances. The regimen should be easy to follow and adjusted when necessary.
- The more predictive onset and duration of action of insulin analogs and premixed insulin analogs can lower the risk of hypoglycemia.
- Basal-bolus (MDI) therapy with a rapid-acting analog 15 minutes before meals and a long-acting insulin analog for basal coverage is effective in patients with advanced β-cell dysfunction and provides patients with flexible insulin dosing based on their lifestyle needs.
- Insulin pens, dosers, pumps, and inhaled insulin have overcome many concerns associated with vial and syringe delivery. These devices should be explained and offered to each patient.
- Where possible, patients should work with a diabetes-care team and be encouraged to take an active role in managing their disease.

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Post-test

1. A1C reflects overall glycemic control and is a function of fasting and postprandial glucose (PPG) exposure over the preceding _____.

   a. 4–6 weeks

   b. 2–3 months

   c. 6 months

   d. 1 year

2. PPG excursions in patients with type 2 diabetes _____.

   a. contribute minimally to overall diurnal hyperglycemia

   b. do not occur in patients with good overall glycemic control (A1C <7.0%)

   c. contribute significantly to A1C levels in patients with mild or moderate hyperglycemia (A1C ≤8.4%)

   d. are best controlled with a long-acting insulin analog administered at bedtime

3. Compared with impaired fasting glucose, the DECODE study showed that inadequate PPG control is a _____ contributor to risk of death.

   a. larger

   b. smaller

   c. similar

4. All of the following statements are true about insulin therapy EXCEPT _____.

   a. insulin can be administered via a pen device

   b. human insulin formulations have more physiologic time-action profiles compared with insulin analogs

   c. insulin therapy is typically initiated after patients do not meet goals with oral antidiabetic drugs (OADs)

   d. risk of hypoglycemia limits the dosage of insulin

5. SW is a 65-year-old African American female diagnosed with type 2 diabetes 6 years ago. She presents complaining of "feeling tired all the time," and having burning pains in both feet. She is asymptomatic of polyuria and polydipsia. Current medications include glyburide 10 mg BID, metformin 500 mg BID (higher doses cause diarrhea), and pioglitazone 45 mg. She has completed a diabetes self-management program in the last 12 months and lost 6 pounds in the last 6 months. She never skips breakfast, and dinner is usually her largest meal of the day. A1C is 8.6%; fasting plasma glucose (FPG) averages 170 mg/dL and PPG averages 200 mg/dL. She is reluctant to start on insulin, but agrees to try it "if it would make me feel better." With a suitable adjustment in OAD therapy, an appropriate starting insulin regimen to address both FPG and PPG values would be _____.

   a. 10 units of a long-acting insulin analog at bedtime

   b. 10 units of a premixed insulin analog at dinner, with the option of adding a second (morning) insulin dose if PPG values are not at target

   c. a rapid-acting insulin analog administered with the largest meal of the day

   d. basal-bolus therapy, including a long-acting insulin analog at bedtime and a rapid-acting insulin analog at any meal with more than 2 servings of carbohydrates

6. All the following are usually considered when initiating insulin therapy EXCEPT _____.

   a. blood glucose levels and A1C

   b. time-action profile of insulin formulation

   c. family history of insulin use

   d. type of insulin delivery system

7. Insulin therapy is eventually required for the majority of patients with type 2 diabetes because _____.

   a. most patients develop intolerance to OADs

   b. adding a second OAD will not reduce A1C levels

   c. weight gain with age increases insulin resistance

   d. exogenous insulin is required as β-cell secretory capacity declines

8. Common concerns for patients starting insulin therapy include _____.

   a. type of insulin formulation

   b. hypoglycemia

   c. weight gain

   d. both b & c

9. Patients with hyperglycemia and _____ should be placed on insulin therapy initially.

   a. FPG >250 mg/dL

   b. ketonuria

   c. hypocalcemia

   d. either a or b

10. DJ, a 50-year-old female with a 10-year history of type 2 diabetes, has recently added insulin to her OAD regimen to improve glycemic control (current A1C is 8.5%). Six days ago, she began administering a biphasic insulin analog, 10 units at breakfast and 10 units at dinner. She has agreed to self-titrate the dose and fax the results to her physician. Over the last 6 days, FPG has averaged 150 mg/dL and PPG has averaged 180 mg/dL. She should _____.

    a. make no change to her daily insulin dose

    b. increase her total daily dose by 2 units

    c. increase her total daily dose by 4 units

    d. increase her total daily dose by 8 units

11. MJ, a 48-year-old male with a 16-year history of type 2 diabetes and BMI of 35 kg/m^2, recently transitioned from a premixed insulin analog twice daily to basal-bolus therapy for better postprandial BG control. He administers 20 units of a long-acting insulin analog at bedtime and rapid-acting insulin analog with each meal. His insulin-to-carbohydrate ratio has been titrated to 1:8. If he estimates that his lunch contains 80 grams of carbohydrates, and his prelunch BG met his target of 110 mg/dL, how much rapid-acting insulin analog should he administer just before lunch?

    a. 8 units

    b. 10 units

    c. 16 units

    d. 20 units

12. Patients who administer a premixed insulin analog at supper always need a bedtime snack to avoid nocturnal hypoglycemia.

    a. True

    b. False

13. EH is a 43-year-old male with a BMI of 33.5 kg/m^2. He was diagnosed with type 2 diabetes 5 years ago and has been on OADs for nearly 5 years. Because EH's A1C level has increased to 9.1%, his physician recommends that he commence insulin therapy. However, EH is very anxious about injections and wants to start with a simple regimen. Based on EH's needs and concerns, which of the following would be a good starting regimen for providing both basal and postprandial coverage?

    a. A long-acting insulin analog QD using vial and syringe

    b. A long-acting insulin analog QD using a pen device

    c. A premixed insulin analog formulation BID using a pen device

    d. A basal-bolus regimen using an injection device or insulin pump

14. EH is now 48 years old with a BMI of 36.5 kg/m^2. Although he had maintained good glycemic control with his insulin regimen that was prescribed 5 years ago, his BG patterns have become more irregular and A1C has increased from 6.9% 1 year ago to 8.6%. Since the diabetes educator determined that EH had been adhering to his treatment and he no longer feared injections, he would achieve the best control of his BG level if his regimen was now changed to _____.

    a. a long-acting insulin analog QD using vial and syringe

    b. a rapid-acting insulin analog BID using a pen device

    c. a premixed insulin analog formulation BID using a pen device

    d. a basal-bolus regimen using an injection device or insulin pump

Practical Approaches to Using Insulin Analogs and Premixed Insulin Analogs in Patients with Type 2 Diabetes (297-999-06-015-H01)

This evaluation and post-test may also be completed online at:
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The participant will be offered an opportunity to print a statement of credit upon successful completion of the post-test (score at least 75%) and evaluation.

Program Evaluation

How many hours ____ and minutes ____ did it take you to complete this CE program?

Please indicate date of completion: _____/_____/_____

DIRECTIONS: Please rate the following on a scale of 1 to 5 (1 = Poor, 5 = Excellent).

Effectiveness of Teaching/Learning Method *(Please circle one response per line.)*

How well did this program achieve the following objectives?	*Poor*				*Excellent*
• Review the prevalence and progressive nature of diabetes and the associated economic implications.	1	2	3	4	5
• Discuss the importance of glycemic control in type 2 diabetes and current strategies for achieving it.	1	2	3	4	5
• Explain how and when to initiate insulin for type 2 diabetes, including advantages and potential barriers.	1	2	3	4	5
• Compare different insulin formulations and regimens for type 2 diabetes, and discuss their appropriateness for different patient types.	1	2	3	4	5
• Review recent advances in insulin technology and the use of diabetes-care teams.	1	2	3	4	5
The relationship of the learning objectives to the overall purpose/goal of this independent study was effective.	1	2	3	4	5
The teaching/learning resources were effective.	1	2	3	4	5
This home study has contributed to my professional effectiveness and improved my ability to:	*Strongly Disagree*				*Strongly Agree*
• Optimize patient's care	1	2	3	4	5
• Communicate with patients	1	2	3	4	5
• Manage my practice	1	2	3	4	5
• Improve my clinical skills	1	2	3	4	5
• Other _____	1	2	3	4	5
	Poor				*Excellent*
The overall program was:	1	2	3	4	5

Do you feel this program covered the topic adequately? ☐ Yes ☐ No

Do you feel that the program was balanced, objective, and free of commercial bias? ☐ Yes ☐ No

Will you change your clinical practice based on this activity? ☐ Yes ☐ No

Suggested topics for future programs: _____

_____

General comments/suggestions: _____

_____

Post-Test Answer Grid *(Enter the correct answer.)*

1. ☐	5. ☐	9. ☐	13. ☐
2. ☐	6. ☐	10. ☐	14. ☐
3. ☐	7. ☐	11. ☐	
4. ☐	8. ☐	12. ☐	

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Scherer Clinical Communications

October 2006

Printed in USA.