



# Insulin Therapy for Type 2 Diabetes:

*Using Insulin Analogs and  
Premixed Insulin Analogs*

*An educational activity approved for continuing education credit  
for physicians, nurse practitioners, and physician assistants*



## Program Goal

The goal of this program is to provide participants with information about the pathophysiology of type 2 diabetes, the need to identify patients who would benefit from insulin therapy, and how to initiate therapy using insulin analogs and premixed insulin analogs.

## Audience

This activity is intended for physicians, nurse practitioners, and physician assistants who care for patients with type 2 diabetes.

## Objectives

After completion of this educational activity, the participant should be able to:

- Explain why postprandial glucose excursions need to be controlled in addition to fasting plasma glucose
- Give examples of when insulin would be given as initial therapy
- Describe two insulin regimens that cover both fasting and postprandial glucose excursions
- Explain how insulin regimens are selected and what factors have to be considered when starting and adjusting insulin
- Discuss how insulin analogs and premixed insulin analogs provide advantages over human insulin formulations
- Describe some common concerns when starting insulin therapy and how these can be overcome

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This program has been approved for 1.4 contact hours of continuing education (which includes 1.4 hours of pharmacology) by the American Academy of Nurse Practitioners. Program ID 0412496.

This program has been reviewed and is approved for a maximum of 1.25 hours of clinical Category I (Preapproved) CME credit by the Physician Assistant Review Panel. Approval is valid for one year from the issue date of March 1, 2005. Participants may submit the self-assessment at any time during that period.



This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

## Term of Approval

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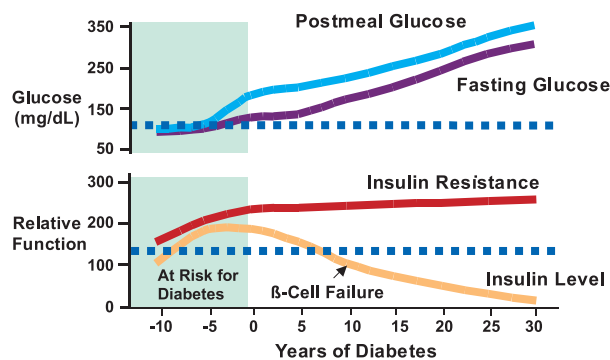
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## INTRODUCTION

Type 2 diabetes is characterized by multiple physiologic and metabolic defects, including impaired  $\beta$ -cell insulin secretory function, insulin resistance, and accelerated hepatic glucose production. Although oral antidiabetic drugs (OADs) are often used for first-line pharmacotherapeutic management of type 2 diabetes, due to the progressive nature of this disease (Fig. 1), many patients will eventually require insulin for optimal glycemic control.<sup>1</sup> Therefore, it is imperative that healthcare professionals caring for patients with type 2 diabetes be aware of the benefits and safety of insulin as well as new advances in insulin formulations and insulin delivery systems. Insulin is the most effective therapy, with the best safety and tolerability profile when dosed properly.<sup>2</sup> Newer formulations, such as insulin analogs and premixed analogs, have overcome many of the shortcomings of the human insulin products.<sup>3-6</sup> The objectives of this monograph are to describe the circumstances under which treatment with insulin analogs and premixed insulin analogs can be initiated in patients with type 2 diabetes, when they should be used, and the proper selection of formulation as well as titration of the dose and adjustment of the regimen.

Figure 1: Progression of Type 2 Diabetes



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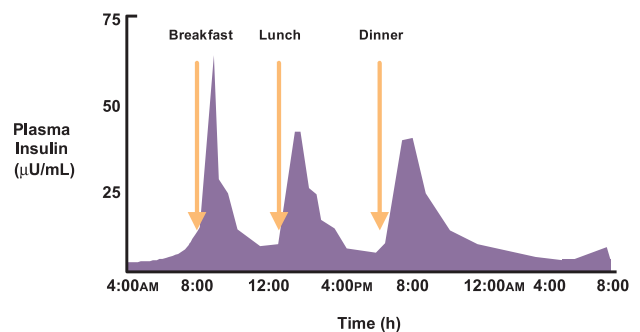
## OPTIMIZING GLYCEMIC CONTROL

In individuals without diabetes, basal secretion of insulin occurs at a steady rate that primarily limits hepatic glucose production and output, while large peaks in insulin secretion occur with meals (Fig. 2).<sup>7</sup> Diabetes is usually diagnosed by any of the following: fasting plasma glucose (FPG)  $\geq 126$  mg/dL, symptoms of diabetes and a random plasma glucose  $\geq 200$  mg/dL, or a 2-hour plasma glucose  $\geq 200$  mg/dL during a 75-gram oral glucose tolerance test.<sup>7</sup> The diagnosis must be confirmed on a separate day unless unequivocal symptoms of hyperglycemia are present.<sup>7</sup> The long-term (>3 months) impact of hyperglycemia on glycemic control is monitored by measuring A1C (glycosylated hemoglobin) levels in the

The normal pancreas steadily secretes insulin between meals (basal insulin) and rapidly releases insulin in response to meals (prandial insulin). Early in the disease process, oral agents may be used to stimulate basal and prandial insulin release. As  $\beta$ -cell dysfunction progresses, insulin injections are required to mimic the normal pattern of insulin secretion to maintain optimal glycemic control and to minimize the risk of diabetes-related complications. Since both basal and prandial insulin are needed to maintain glycemic control, most patients with diabetes and severe  $\beta$ -cell dysfunction will need both basal and prandial insulin injections.

blood. A1C is usually <6% in individuals without diabetes. An increase of 1% in A1C corresponds to an increase in mean plasma glucose of  $\sim 35$  mg/dL.<sup>8</sup> A1C is not recommended for the diagnosis of diabetes.<sup>7</sup>

Figure 2: Physiological Serum Insulin Secretion Profile in Individuals Without Diabetes



Adapted with permission from White JR, Jr., Campbell RK, Hirsch IB. Novel insulins and strict glycemic control. Analogues approximate normal insulin secretory response. *Postgrad Med.* 2003;113:30-36. ©The McGraw-Hill Companies.

Although postprandial glucose excursions (ie, high blood glucose [BG] levels after meals) are a substantial contributor to daytime hyperglycemia, most therapies are based on fasting glucose measures.<sup>8</sup> Data from several observational studies, including the Third National Health and Nutritional Examination Survey (NHANES III), have shown that postprandial hyperglycemia is common even in those patients with type 2 diabetes who have good overall glycemic (A1C) control.<sup>9</sup>

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study has shown that inadequate control of postprandial glycemia (PPG), which is primarily due to impaired first-phase insulin secretion, is a larger risk factor for cardiovascular disease and death from all causes than impaired fasting glucose.<sup>10</sup> The importance of PPG was reinforced by a study that showed that glucose excursions after breakfast were a major contributor to failed glycemic control in patients with type 2

diabetes receiving OAD therapy.<sup>11</sup> In another study of 290 patients with type 2 diabetes who were poorly controlled with two OADs, postprandial glucose excursions were predominant in those with mild or moderate hyperglycemia compared with patients with severe disease (ie, A1C >8.4%).<sup>12</sup> As patients get closer to their target A1C levels, elevations in PPG have a much greater impact on A1C compared with FPG.<sup>12</sup> Therefore, both fasting and postprandial glucose excursions should be considered in the management of diabetes.

## TREATMENT APPROACHES AND CONSIDERATIONS FOR INSULIN THERAPY

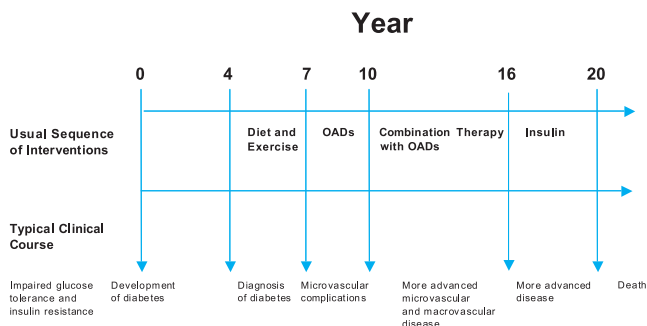
### The Current Stepwise Therapeutic Approach

The management of type 2 diabetes generally is approached in a stepwise manner, beginning with lifestyle modifications (meal planning and exercise), monotherapy with an OAD, combination OAD therapy, and insulin therapy, either in combination with an OAD or alone to achieve and maintain optimal glycemic control (Fig. 3). Various classes of pharmacotherapeutic agents are available for the treatment of type 2 diabetes. Each class has specific sites of action to improve glycemic control, and a combination of agents can produce additive effects by targeting the multiple dysfunctions in type 2 diabetes. In general, OADs lower A1C by 1% to 2% as monotherapy or when added as a second or third agent.<sup>13, 14</sup> On the other hand, insulin can be dosed to lower A1C to a desired target, providing hypoglycemia does not occur, but its use is often initiated only after failure of OAD regimens.

The success of the stepwise approach depends on the aggressiveness of monitoring and stepping up to the next agent when the targeted goals are not met.<sup>15</sup> However, a major limitation on the clinical success of this method is that long periods of inadequate control often occur before the next therapeutic step is introduced.<sup>16</sup> Consequently, the evidence indicates that this stepwise approach is not working in the United States, as most Americans with diabetes are not meeting treatment goals for glycemic control. The number of patients meeting the American Diabetes Association (ADA) goal of A1C <7.0% has declined from 44.5% in 1994 to 35.8% in 2000.<sup>17</sup> Furthermore, the majority of patients are not being sufficiently monitored for glycemic control and complications at the recommended frequency. In an analysis of data collected from NHANES III and the Behavioral Risk Factors Surveillance System from 1988 to 1994, only 29% of the 4,085 study participants with diabetes had an A1C test, 63% had a dilated eye examination, and 55% had a foot examination during a 1-year observation period.<sup>18</sup>

This occurred despite the fact that many of these patients had additional risk factors for vascular complications of diabetes: 34% had hypertension and 58% had elevated low-density lipoprotein cholesterol levels. These observations support the need for more aggressive management of diabetes, including modification of treatment as soon as patients fail to meet glycemic targets.

Figure 3: Stepwise Approach Used for the Treatment of Type 2 Diabetes



Adapted with permission from Nathan DM. *New Engl J Med.* 2002;347:1342-1349. ©2002 Massachusetts Medical Society.

### The 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.<sup>19, 20</sup> Many patients with type 2 diabetes will have some evidence of macrovascular or microvascular complications by the time diabetes is diagnosed.<sup>21</sup> Epidemiologic analyses of data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that each percentage point decrease in A1C correlated with substantial reductions in the risk for both microvascular and macrovascular complications.<sup>22</sup> Based on these landmark trial findings,<sup>19, 20, 22</sup> both the ADA<sup>7</sup> and the American Association of Clinical Endocrinologists (AACE)<sup>23</sup> have set aggressive targets for control of BG. The ADA recommends an A1C target of <7.0%, whereas the AACE goal for A1C is ≤6.5%.

### When to Consider Insulin

Patients with poorly controlled diabetes have high morbidity and mortality rates, poor quality of life, and incur higher healthcare costs.<sup>13</sup> Therefore, it is essential that patients maintain glycemic control and be treated with safe and effective regimens in a timely manner.

Exogenous insulin is needed when severe insulin resistance is present, when  $\beta$ -cell capacity falls below a critical threshold, and when glycemic control is no longer adequate with OADs.<sup>24</sup> This is particularly important in patients who present with severe symptomatic hyperglycemia (FPG >350

mg/dL) and ketonuria.<sup>25</sup> In some cases, OADs may be contraindicated; therefore, insulin is initiated at the time of diagnosis.

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. At present, many patients have had type 2 diabetes for 10 to 15 years (and may have developed complications) before insulin therapy is initiated.<sup>16</sup> Due to the progressive nature of type 2 diabetes, many patients will eventually require insulin therapy. In the UKPDS, more than half of the patients with type 2 diabetes required insulin at the end of the 10-year study, and the investigators predicted that most patients would need insulin during their lifetimes.<sup>1</sup> Some authorities advocate that type 2 diabetes be treated aggressively by introducing insulin earlier in the treatment plan.<sup>13, 26</sup>

The main limitation of insulin therapy is its potential to cause hypoglycemia, which can often be overcome by careful monitoring of BG and adjustments of insulin doses or the meal plan. Patients should be referred to diabetes self-management training programs to learn skills to prevent and treat hypoglycemia, monitoring of BG, and insulin dose adjustment. Depending on the nature of the glucose excursions and severity of the disease, insulin can be used in combination with OADs or alone. Availability of insulin analogs and premixed insulin analogs, as well as development of more convenient insulin delivery systems, has alleviated some barriers and fears associated with insulin use.<sup>26</sup>

## INITIATING INSULIN THERAPY IN PATIENTS WITH TYPE 2 DIABETES

### Insulin Analogs and Premixed Insulin Analogs

The development of insulin analogs has been one of the greatest advances in diabetes therapy in the last decade.<sup>3</sup>

As shown in Table 1, several formulations of insulin analogs and premixed insulin analogs are available. Insulin analogs were developed to more closely mimic physiologic secretion; they have a more predictable onset and duration of action compared with human insulin formulations. The development and use of insulin analogs has also increased flexibility for dosing and mealtimes.<sup>3</sup> Insulin aspart and insulin lispro are rapid-acting analogs that are administered just prior to meals whereas insulin glargine is a long-acting analog used for basal control (Table 1). Insulin glulisine, a rapid-acting analog, was recently approved by the US Food and Drug Administration (FDA) but is not yet available in the United States. Insulin detemir is a long-acting analog that is available in Europe and is awaiting FDA approval in the United States.

Premixed insulin analogs provide both basal and prandial coverage in one injection. Two products are currently available: (1) biphasic insulin aspart 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart); and (2) biphasic insulin lispro 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro). The rapid-acting components of premixed analogs are more rapidly absorbed and provide better postprandial coverage compared with insulin premixed formulations containing Regular insulin.<sup>6</sup> Because of their more physiologic time-action profiles, insulin analogs and premixed insulin analogs may also lower the risk for hypoglycemia, especially overnight, compared with human insulin formulations.<sup>4-6, 34</sup>

### How to Initiate Therapy

Individualized BG targets are usually established for each patient. The aim of insulin therapy is to achieve optimal glycemic control without causing hypoglycemia or excessive weight gain. When initiating insulin therapy, many patients remain on their OADs but the doses are gradually reduced and sometimes the OADs are discontinued. This decision is made on a case-by-case basis and some examples are included in the case studies in this monograph. The insulin dose can

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 to Peak Action (hr)	Duration of Action (hr)
<b>Rapid-Acting Analogs</b>			
Insulin lispro (Humalog®)	0.25-0.5 <sup>27</sup>	0.8-4.3 <sup>28</sup>	4-6 <sup>27</sup>
Insulin aspart (NovoLog®)	<0.5 <sup>29</sup>	1-3 <sup>30</sup>	3-5 <sup>30</sup>
<b>Long-Acting Analogs</b>			
Insulin glargine (Lantus®)	1 <sup>31</sup>	Peakless <sup>31</sup>	10.8-24 <sup>31</sup>
<b>Premixed Insulin Analogs</b>			
Biphasic insulin lispro 75/25 (Humalog® Mix75/25)	<0.5 <sup>32</sup>	1-6.5 <sup>32</sup>	~22 <sup>32</sup>
Biphasic insulin aspart 70/30 (NovoLog® Mix 70/30)	<0.5 <sup>33</sup>	1-4 <sup>33</sup>	≤24 <sup>33</sup>

Wide interindividual variation in time to onset of action, time to peak action, and duration of action can occur.

be titrated slowly over several weeks as necessary to achieve optimal glucose levels. The regimen should be simple and tailored to match the patient's needs and lifestyle, including eating patterns and activity level. The contributions of fasting and postprandial glucose excursions to overall hyperglycemia should also be considered.

Other issues that need to be addressed when initiating insulin therapy include the type(s) of insulin formulation, the number of injections, and the insulin delivery system that is appropriate for a particular patient. The following points should be considered when choosing an insulin formulation: how rapidly it works (onset), when it works at maximum capacity (peak), how long it works (duration), and impact on lifestyle. The predictability of these properties and the stability of the different formulations in various insulin delivery systems should also be considered. Variable absorption of human insulin formulations has been a major limitation.<sup>3</sup> This is less of an issue with insulin analogs and premixed insulin analogs because they have more predictable time-action profiles.

In clinical studies and in everyday practice, many clinicians empirically start with a low fixed dose of insulin. Algorithms used to estimate insulin doses vary.<sup>3, 14, 35-39</sup> The starting regimen is determined primarily by the degree of hyperglycemia as measured by BG monitoring and the A1C value. Body weight is also used to calculate the appropriate starting insulin dose. Based on home glucose monitoring, the dose used is then titrated every few days or weekly by the clinician by telephone or during brief office visits.<sup>40</sup> Beginning at a low dose and slowly titrating to higher doses helps to avoid hypoglycemia and builds patient confidence when initiating insulin therapy. Healthcare providers should explain to patients that the dose and number of injections would be raised over time as the disease progresses. They should also point out that some degree of disease progression is normal and not due to "failure" of the patient to adhere to the treatment plan. The following characteristics and such issues as BG levels, carbohydrate counting, and body weight can be considered when calculating the starting insulin dose and making dose adjustments.<sup>35</sup> These will be utilized in the case studies at the end of this program.

### **Blood Glucose Levels**

BG monitoring is essential for evaluation of the prescribed regimen. A reasonable plan involves checking at least one fasting and one postprandial BG value and recording each result. The frequency and timing of BG testing depends primarily on the insulin regimen. The patient can record each result, preferably using a meter with memory and

download capability. The frequency of monitoring also depends on the severity of hyperglycemia, magnitude of glucose excursions, patient willingness, and insurance coverage. Those using multiple daily injection (MDI) therapy may need to check the BG level before each meal, occasionally 2 hours postprandial, and at bedtime each day.

Using a system of patterned testing, the individual can test less frequently but still obtain data to assess the efficacy of the regimen. Finger sticks could be done for 3 days; before and after one meal to determine the impact of the premeal insulin dose. The meal selected should vary so that at the end of the assessment period, each meal is studied at least once. Testing overnight and the next morning provides information concerning the impact of the basal insulin.

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. The use of these patterns will be illustrated in the case studies presented at the end of this monograph.

### **Carbohydrate Counting and Adjustment of Mealtime Insulin Doses**

Carbohydrate counting is a skill that adds flexibility to meal planning. Patients using MDIs or an insulin pump can adjust the mealtime insulin dose based on the estimated carbohydrate content of the meal as well as the BG reading.<sup>38</sup> For example, 1 unit of a rapid-acting analog can be given for every 10 to 15 grams of carbohydrate consumed.<sup>41</sup> This strategy works for basal-bolus therapy but is not appropriate for patients using a premixed analog formulation. A registered dietitian or diabetes educator can assist patients with carbohydrate counting and formulas for calculating dose adjustments.

An obese individual may need a ratio of 1:5 (1 unit of a rapid-acting insulin analog for every 5 grams of carbohydrate to be consumed) whereas a thin, insulin-sensitive individual may require a ratio of 1:20. BG should be checked 2 hours after the meal to determine if the dose is correct. Postprandial BG should be within 30 to 60 points of the preprandial value when the insulin:carbohydrate ratio is optimal.

If the premeal glucose level is high, more (supplemental) insulin may be given in addition to the usual prandial insulin dose. The extra insulin will vary according to a patient's sensitivity to insulin. For example, patients may require an additional 1 to 2 units for every 50 mg/dL that the premeal glucose level is above the target.<sup>38</sup>

For example, a patient uses an insulin:carbohydrate ratio of 1:15. He is about to eat dinner, which he estimates contains 90 grams of carbohydrate. 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. He will take 6 units of insulin aspart to cover the 90 grams of carbohydrate (90 grams carbohydrate/15) plus another 2 units of insulin aspart to correct being 100 mg/dL over his target glucose level. His total insulin dose with dinner will be 8 units.

### Body Weight

Overweight patients require higher doses of insulin because of greater insulin resistance and deficiency. Although 0.4 to 0.8 unit/kg can be used as an initial daily dose in overweight patients, many patients with type 2 diabetes need a total daily dose of 1.0 to 1.2 units/kg to achieve an A1C <7.0%.<sup>37</sup> The initial dose is increased by 2- to 4-unit increments (or by 5- to 10-unit increments in patients with severe insulin resistance) every 3 to 4 days until the desired level of control is achieved.<sup>39</sup>

For example, a patient with a body mass index (BMI) of 46 and an A1C of 9.6% was initiated on insulin therapy at her last visit. Based on her high BMI and likely insulin resistance, her clinician determined that 0.8 unit/kg was an appropriate starting dose. At a follow-up visit several months later, her A1C was better (8%), but not below their agreed upon target (<7%). Her total daily dose was then titrated to 1.0 unit/kg which decreased her A1C to 7.2%.

### Special Considerations

Dose adjustments may be required if the patient is taking medications that can affect carbohydrate metabolism or responses to insulin. 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.

## ADDITIONAL CONSIDERATIONS

### Addressing Patient Concerns

Despite increasing or uncontrolled BG and A1C, patients resist insulin for a variety of reasons (Table 2).<sup>42</sup> The healthcare provider can assist patients in making an informed decision by understanding their concerns and providing the information they require.<sup>42</sup> Table 2 lists some common concerns and strategies that can help patients overcome these issues.

### A Diabetes-Care Team Approach

Because diabetes is a multifaceted disease, a multidisciplinary team approach to disease management is recommended. However, in primary care practice, where the majority of patients are treated, the physician may lack the time and resources to instruct and educate patients. Collaboration with diabetes educators and other healthcare professionals should be part of the standard of care for patients with diabetes.

The patient should be involved in all aspects of care including the choice of therapy. Many concerns about insulin therapy

Table 2. **Common Concerns in Patients Starting Insulin Therapy**

Concern	Resolution
Initial anxiety	Enhance education regarding the benefits of insulin in treating diabetes. Determine current beliefs, past experiences.
Feeling of personal “failure”	Inform patient that diabetes is a progressive disease and explain $\beta$ -cell failure.
Hypoglycemia	Educate about the signs and symptoms as well as prevention and treatment. Provide details regarding the meal timing requirements of the insulin plan. With prandial insulin, specify matching the insulin dose to what the patient plans to eat (ie, amount of carbohydrate) and what the patient can eat that will have no effect on the glucose level (ie, protein, fat).
Injection phobia	Teach self-injection with saline. Explain devices including those that conceal the needle as well as availability of fine needles.
Weight gain	Explain improved metabolic control and efficiency. Adjust food portions and physical activity. Carefully plan snacks as part of the 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 provide educational materials/programs 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. Emphasize hyperglycemia causes the complications.

are manageable and can be prevented by careful consultation, monitoring, and dose adjustments.

A team of healthcare professionals working with patients with diabetes are more likely to lead the patient through the complexities of insulin therapy and help them solve problems than having one clinician as the sole resource. In addition to insulin administration skills and options, patients also need to learn recognition, prevention, and treatment of hypoglycemia; exercise guidelines and precautions; meal planning and carbohydrate counting; and weight management. The skills involved in making adjustments for exercise, travel, during sickness, and when under stress are also part of a diabetes education 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 to feed the peaks of insulin therapy can add unnecessary calories. Patients can work with registered dietitians to minimize any weight gain due to more efficient metabolism or snacking.

Additional information for the diabetes team and patient is available from the following:

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>

### 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.<sup>43</sup> Patients who were once limited to the single option of vial and syringe delivery now have the choice of reusable (“durable”) or prefilled (“disposable”) insulin pens, insulin jet injectors, insulin dosers, 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 compact insulin pumps enables discreetness and as-needed delivery of insulin (basal-bolus), obviating the necessity for multiple injections.

## CASE STUDIES

Eight case studies are presented here to illustrate various situations that the clinician may encounter in treating patients with type 2 diabetes and to describe the various treatment options involving insulin regimens.

The following cases provide examples of varying patient scenarios where adequate glycemic control using OADs was not achieved.

### Coverage of PPG and FPG with a Premixed Insulin Analog

Since the main aim of insulin therapy is to correct the physiologic deficit and mimic endogenous secretion without causing hypoglycemia,<sup>34</sup> both PPG and FPG should be targeted. Premixed insulin analogs cover both PPG and FPG with the same injection. A premixed formulation can be administered once or twice a day, sometimes in conjunction with OAD therapy.

#### Case 1: Patient was not maintaining glycemic control with combination OAD therapy, so premixed insulin analog therapy was initiated

CJ is a 59-year-old female in whom type 2 diabetes was diagnosed 10 years ago. She is 5'9" tall, weighs 168 pounds, and has a BMI of 25. CJ works full time and commutes 40 to 60 minutes per day depending on traffic. She works in a sales department, so her meal breaks during work hours are not set. Dinner at home is her largest meal of the day. CJ has also stated that she has no time for exercise and that she is really too tired to even consider it.

CJ was initially treated with metformin 500 mg BID and then repaglinide 2 mg TID was added. Two years ago, pioglitazone 15 mg QD was started. With each additional OAD, CJ had a 0.5% to 1% reduction in her A1C values. Her most recent OAD regimen included metformin 1000 mg BID, repaglinide 4 mg with meals, and pioglitazone 45 mg QD.

At a regular visit several months ago, CJ complained of nocturia, polyuria, and polyphagia. Her body weight had also increased 15 pounds over the last 6 months. CJ's fasting blood glucose (FBG) level was 180 mg/dL and postprandial values were >300 mg/dL. Her A1C value was 8.2%. She is hesitant to begin insulin therapy.

#### Comments

This patient is not achieving adequate glycemic control on three OADs. While FBG is high, the postmeal readings are even more markedly abnormal. The A1C of 8.2%

suggests that the hyperglycemia may be related to high postmeal excursions.<sup>12</sup> Meals are inconsistent in both timing and portions.

There are several options for initiating insulin therapy:

1. 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. Given that the patient is taking insulin only once per day, the OADs should be continued to provide coverage for meals other than dinner.

This regimen provides both prandial and overnight basal insulin coverage with a single injection. A pen or doser can administer the insulin within 15 minutes before a meal. The premixed analog formulation eliminates mixing errors, which are possible with an insulin-naïve patient; however, the fixed ratio of rapid- and intermediate-acting analogs precludes the independent adjustment of the basal and prandial components. A fixed meal (size and time) is required and a bedtime snack to prevent nocturnal hypoglycemia may also be necessary.

2. Prescribe long-acting insulin analog (eg, insulin glargine) with the option to add a rapid-acting insulin analog if PPG is not controlled. OAD therapy should be maintained as is. The secretagogues in particular will help with endogenous insulin release with meals. This strategy provides basal insulin coverage for up to 24 hours with a single injection and reduces the risk of hypoglycemia related to eating less than planned. However, basal insulin alone cannot cover postmeal excursions, particularly as  $\beta$ -cells decline. A rapid-acting insulin may then be required.
3. Prescribe mealtime rapid-acting insulin analog (eg, insulin aspart or insulin lispro) with the option to add a long-acting insulin analog if FPG is not controlled. Metformin and pioglitazone therapy should be continued; however, repaglinide should be discontinued. This option may be less favorable to the patient because it requires a dose of insulin before each meal and does not provide basal coverage. On the other hand, advantages include the ability to use a pen or doser for insulin administration, a greater impact on A1C, and less restrictions regarding when and what the patient eats.

Although any of these three regimens are viable options for initiating insulin therapy, the healthcare provider and the patient decide on the first regimen, because it is simple and

has the potential to control both the postprandial and basal glucose excursions in one injection. CJ decided to administer one injection of a premixed insulin analog just prior to dinner (her largest meal) and to consume a bedtime snack to minimize the risk of nocturnal hypoglycemia. A diabetes educator assisted CJ in planning dinner choices to ensure a consistent carbohydrate intake and suggested a realistic plan to increase physical activity. After 3 months, CJ's FPG level had decreased to 110 mg/dL, PPG readings were usually <140 mg/dL, and A1C had decreased to 6.9%. CJ was asked to check her BG levels 2 hours after breakfast and lunch. CJ reported that she has reduced her portions of food, has more energy, and now is walking 30 minutes three times a week. CJ was counseled that she may have to use two injections of the premixed analog to lower her A1C further as  $\beta$ -cell function decreases over time.

### **Case 2: Patient had experienced adverse events with OADs and was switched to a premixed insulin analog formulation**

LJ is a 66-year-old female with a BMI of 27 and a 7-year history of type 2 diabetes. Her most recent A1C was 9.9% and, as a result, metformin 500 mg BID was added to glyburide 10 mg BID. LJ follows a meal plan that consists of routine mealtimes with fixed amounts of food. LJ's day-to-day activities do not vary much. She monitors her BG levels 2 to 3 times daily and reports that her FPG levels average 147 mg/dL, premeal levels average 173 mg/dL, and postmeal levels average 235 mg/dL. However, since metformin therapy was begun, she reports intolerable gastrointestinal side effects. After discussing therapeutic options with this patient, OADs were discontinued, and a premixed insulin analog BID regimen was initiated. After 4 weeks, her doses were stabilized at 20 units, 15 minutes before breakfast and dinner. After 3 months of this regimen, the patient's FPG levels averaged 125 mg/dL, her PPG levels averaged 180 mg/dL, and her A1C decreased to 7.5%.

### **Comments**

Premixed insulin analogs can be an appropriate choice for patients who have a routine lifestyle. The A1C value should be checked in another 3 months and a dose adjustment or change in her treatment regimen may be required if the A1C goals are not met.

For some patients, glyburide could be continued. This may lower the dose of insulin required. As  $\beta$ -cell failure progresses, MDI therapy may be required. If so, glyburide would be discontinued.

**Case 3: Patient was successfully treated with a premixed insulin analog formulation and both PPG and FPG were monitored**

RP, a 57-year-old female with a BMI of 33.2, was diagnosed as having type 2 diabetes 9 years ago. She has a history of retinopathy and nephropathy. RP 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 the dietary recommendations. At presentation, RP's medications included lisinopril 5 mg QD and glipizide 10 mg BID. Previous gastrointestinal side effects experienced with metformin precluded its use. Her A1C at this visit was 11.5%; 1 year ago it was 7.8%. Serum chemistry tests revealed normal renal and liver function.

RP 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 70% intermediate-acting insulin aspart protamine suspension, which provides basal coverage, and 30% rapid-acting insulin aspart, which has prandial action. The insulin dose was titrated, based on BG monitoring results given to the physician by telephone, to 20 units in the morning and 22 units in the evening. She returned to the office a few weeks later with the decreased BG levels reported in Table 3.

Six months later, her A1C value was 7.4%.

Table 3. Blood Glucose Levels in Case 3 Patient

Before Day	Before Breakfast (mg/dL)	Before Lunch (mg/dL)	Dinner (mg/dL)	Bedtime (mg/dL)
Sunday	213	147	166	193
Monday	146	108	115	84
Tuesday	260	129	*	98
Wednesday	130	70	*	129

\*Blood glucose checks not performed.

**Comments**

This patient with long-standing type 2 diabetes and microvascular complications presented with severe, symptomatic hyperglycemia. Due to the severity of her BG elevation, she was prescribed a BID regimen of a premixed insulin analog. A low dose was selected initially to avoid hypoglycemia. Dosages can easily be titrated as necessary by having the patient call the clinic with BG results and with

follow-up at subsequent office visits. The patient needs to be instructed not to skip meals, as the prandial component of her insulin regimen may cause hypoglycemia. Additional dose titration will be necessary to reduce the A1C further as the fasting levels are still elevated.

**Initial Coverage with a Long-Acting Insulin Analog**

Another common way to begin insulin therapy is to add a long-acting insulin analog to OAD therapy at bedtime. Individual dose requirements can vary considerably depending on the degree of endogenous insulin deficiency; therefore, dosing should be based on treatment goals (ie, FPG levels between 90 and 130 mg/dL).<sup>39</sup> As these basal regimens do not cover the postprandial glucose excursions, OADs or a rapid-acting insulin analog may need to be added. Importantly, basal insulin analogs, such as insulin glargine, do not last for 24 hours in all patients.<sup>5</sup>

**Case 4: Patient with elevated A1C and neuropathy on high doses of OADs was successfully treated with a long-acting insulin analog formulation**

JT is a 53-year-old male with a 3-year history of type 2 diabetes. He is 5'11" tall with a BMI of 30. His A1C value is 8% on a high-dose combination OAD regimen consisting of metformin 1000 mg BID, glyburide 10 mg BID, and rosiglitazone 4 mg BID. JT is very concerned because a recent eye examination showed early retinopathy. Because he travels frequently with his job, mealtimes, exercise, and BG monitoring are erratic. A review of his glucose meter's memory revealed that JT had checked his BG levels only 7 times in the past month. JT is now willing to do whatever it takes to get his BG levels under control. After explaining the therapeutic options, his regimen was changed to insulin glargine 10 units at bedtime and metformin 1000 mg BID plus rosiglitazone 4 mg BID during the day. He also met with a registered dietitian to design a meal and exercise plan to fit his lifestyle.

After 1 month of this new regimen, JT's FPG averaged 120 mg/dL and PPG averaged <180 mg/dL. After 3 months, his A1C was 6.8%.

**Comments**

Since postprandial hyperglycemia can significantly contribute to A1C, JT may eventually require a rapid-acting insulin analog after each meal or a twice-daily premixed insulin analog if the OAD therapy does not continue to provide optimal PPG control.

**Case 5: Patient was successfully treated with a long-acting insulin analog formulation but required an OAD for prandial control**

CZ is an obese (BMI, 46) 56-year-old female who presented with a 6-year history of type 2 diabetes and insulin resistance. Her FPG and A1C levels were both elevated at presentation (161 mg/dL and 9.6%, respectively). CZ was taking a combination of glyburide 10 mg and metformin 1000 mg BID as well as medication for hypercholesterolemia and hypertension. Due to the degree of hyperglycemia, a long-acting insulin analog was prescribed at bedtime, and glyburide therapy was discontinued. Her meal plan also was modified to reduce portions and improve variety. After 2 weeks, CZ's FPG levels were consistently <130 mg/dL. At a diabetes education class 1 month later, CZ's postprandial BG was 327 mg/dL after she drank a regular soft drink. CZ was very surprised by this reading, because she was accustomed to fasting readings <130 mg/dL. CZ began PPG monitoring. Even when her food choices were within her meal plan, her postprandial readings were out of range and repaglinide 4 mg was initiated at breakfast and dinner. After 3 months, her FPG range was 100 to 114 mg/dL, PPG range was 141 to 157 mg/dL, and A1C was 7.2%.

**Comments**

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

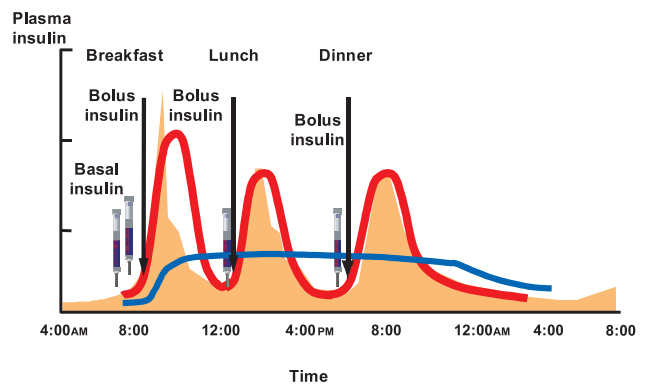
**Basal-Bolus Multiple Daily Injection Therapy**

Basal-bolus therapy attempts to mimic basal and postprandial insulin secretion. These regimens are now being used to aggressively control BG levels in patients with advanced  $\beta$ -cell deficiency and complications. Successful use of basal-bolus therapy requires comprehensive patient education, including the use of carbohydrate counting and correction factors to adjust insulin dosages.

An MDI regimen often includes a rapid-acting insulin analog before each meal and a long-acting insulin analog once a day (Fig. 4). Therefore, patients can coordinate the timing

of injections with meals, giving them more flexibility with mealtimes and lifestyle. BG levels should be monitored frequently to determine the impact of meal content, particularly carbohydrates, on the dose of insulin required. An insulin pump can be used in place of an MDI in patients who are suitable candidates for continuous subcutaneous insulin infusion (CSII) therapy.

**Figure 4: Representation of Rapid-Acting and Long-Acting Insulin Analog Time-Action Curves**



**Case 6: Patient with elevated A1C despite aggressive OAD therapy reluctantly started basal insulin therapy, and ultimately required MDI therapy to achieve optimal glycemic control**

SM is a 60-year-old female with a BMI of 26.5 (height, 5'5"; weight, 159 lb). She was diagnosed with type 2 diabetes 6 years ago. SM reported that her BG levels, checked at home upon waking and at bedtime as well as after each meal, were in the range of 200 mg/dL before meals and 350 mg/dL after meals. She reported making healthy food choices and a regular exercise routine that included walking 4 to 5 times a week for 30 minutes. SM described burning pains in both feet at night. Her current pharmacotherapeutic regimen consisted of glyburide 10 mg BID and metformin 500 mg BID. In the past, higher doses of metformin had caused diarrhea. Pioglitazone 30 mg also had been prescribed in the past, but was discontinued because of pedal edema. Her A1C was 9.3%.

SM was reluctant to start insulin therapy but ultimately agreed. Therapy was initiated with insulin glargine 10 units once daily at bedtime. The dose was titrated upward based on BG monitoring results reported by SM to the clinic by telephone. At a follow-up visit 3 weeks later, SM reported administering insulin glargine 30 units at bedtime and continuing OADs. FPG levels were between 70 and 100 mg/dL, but PPG levels were all >250 mg/dL. Her physician

suggested supplementing with insulin aspart, beginning with one injection of 10 units with her largest meal of the day. She agreed and subsequently discovered that her BG excursions were better controlled if she administered the insulin aspart with all of her meals. Glyburide was discontinued.

SM met with a diabetes educator and learned how to use a pen device for delivering insulin aspart and received additional education regarding healthy meal choices, ways to minimize weight gain, and carbohydrate counting so that she could adjust the insulin aspart dose. She carries her insulin pen with her wherever she goes, is very pleased with her ability to manage her BG, and does not mind administering insulin 4 times per day. After 3 months, her FPG levels averaged 113 mg/dL and her PPG levels averaged 153 mg/dL. Her A1C had decreased to 6.9%.

### Comments

Patients who need multiple injections of insulin can begin with a once-daily injection of a long-acting insulin analog with subsequent addition of a rapid-acting insulin analog at mealtimes. An adjustment of the long-acting analog may be required if FPG is too low or if nocturnal hypoglycemia is suspected. 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 7: Patient using premixed insulin analog regimen improved glycemic control after switching to an MDI regimen

MS is a 65-year-old recently retired businessman in whom type 2 diabetes was diagnosed 10 years ago. He has a history of hypertension and hyperlipidemia, which are well controlled with medication and healthy food choices. At the last ophthalmology visit, proliferative retinopathy was observed.

For the past 2 years MS has been using a premixed insulin analog (biphasic insulin aspart 70/30). 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 he plays golf with his friends.

His BG levels over the past week were as shown in Table 4.

On Monday, MS 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 symptoms of hypoglycemia, which resolved with a snack and some juice. His A1C at a recent visit was 7.9%.

MS and his physician agreed that 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 a day. The physician prescribed insulin glargine 40 units every evening and insulin aspart 10 to 15 units with each meal. This provided him with 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 advanced carbohydrate counting skills.

### Comments

In patients with long-standing type 2 diabetes and advanced  $\beta$ -cell dysfunction, an MDI insulin regimen provides the most physiologic insulin replacement. With a 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.

Table 4. **Blood Glucose Levels in Case 7 Patient**

Day	Before Breakfast (mg/dL)	Before Lunch (mg/dL)	Before Dinner (mg/dL)	Bedtime (mg/dL)	3:00am (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.

Various easy-to-use insulin delivery systems can be used to administer the rapid-acting insulin analog in a convenient and discreet manner.

**Case 8: Patient using a premixed human insulin formulation presented with hypoglycemia and was switched to a basal-bolus regimen**

DT is a 57-year-old African American male in whom type 2 diabetes was diagnosed 12 years ago. He travels frequently for his job and finds it difficult to eat his meals on time and make dose adjustments to his insulin regimen for the amount of food that he eats at each meal. DT's last A1C was 9.0%. He was administering 60 units of premixed human insulin 70/30 before breakfast and an additional 30 units before dinner. DT 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 at mealtimes and in his lifestyle.

Therapy was changed to 40 units of a long-acting insulin analog at bedtime with additional recommendations to use 1 unit of a rapid-acting insulin analog for every 15 grams of carbohydrate eaten at each meal. After 3 weeks, his average BG values were as shown in Table 5. To determine if the insulin:carbohydrate ratio is correct, DT was advised that the 2-hour PPG level should be within 30 to 40 mg/dL of the premeal value.

Table 5. **Blood Glucose Levels in Case 8 Patient**

Blood Glucose Checks	Values (mg/dL)
Fasting blood glucose	123
2 hrs after breakfast	155
Before lunch	103
2 hrs after lunch	185
Before dinner	115
2 hours after dinner	169

DT was concerned because his 2-hour PPG values were still greater than his target goal of 140 mg/dL. Based on discussions with DT's primary care physician and registered dietitian, the recommendation to use 1 unit of rapid-acting analog was changed from every 15 grams of carbohydrate at each meal to every 12 grams. It was also recommended that he keep a food diary and compare BG levels after meals so the optimal insulin:carbohydrate ratio could be determined. By following these recommendations, he met his fasting, premeal, and postprandial BG goals. After 3 months, his A1C had been reduced to 8.1%. The more rapid action and duration of activity of the rapid-acting analog formulation may have helped to resolve his problems with hypoglycemia.

**Comments**

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 levels. Further adjustments will be necessary to get A1C to <7.0% or ≤6.5%.

## SUMMARY

Type 2 diabetes is characterized by multiple physiologic and metabolic defects relating to insulin and glucose production and usage.  $\beta$ -cell deficiency is an inevitable consequence of type 2 diabetes. Thus, many patients will eventually require insulin for optimal glycemic control. In some cases (eg, severe hyperglycemia/ketonuria or when OADs are contraindicated), insulin may be the first choice to manage diabetes.

Exogenous insulin is necessary when insulin resistance is present, when  $\beta$ -cell capacity falls below a critical threshold, and when glycemic control is no longer adequate with OADs.

Both basal and postprandial glucose excursions contribute to overall glycemic control. Thus, target FPG and PPG levels need to be identified and monitored routinely. 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 and titrate up every 3 to 4 days based on BG readings and meal carbohydrate content until goals are achieved. Insulin regimens must be tailored to achieve glycemic control while minimizing the risk of hypoglycemia and other metabolic disturbances. They should be easy for patients to follow and adjust when necessary based on BG readings and the carbohydrate content of meals. The more predictive onset and duration of action of insulin analogs and premixed insulin analogs can increase dosing flexibility and may lower the risk of hypoglycemia.

The availability of various insulin analogs and premixed insulin analogs along with a variety of insulin delivery devices has enhanced the ease of use and acceptability of insulin for the management of type 2 diabetes. Basal-bolus therapy with a rapid-acting analog administered 15 minutes before meals and a long-acting insulin analog for basal coverage is effective in patients with advanced  $\beta$ -cell dysfunction and provides patients with flexible insulin dosing. Insulin pens, dosers, and pumps have overcome many concerns associated with vial and syringe delivery. These devices should be explained and offered to each patient.

Pharmacotherapy is one aspect of maintaining optimal glycemic control in type 2 diabetes. Exercise, nutrition, and effective management of comorbid conditions all contribute to glycemic outcomes and complications in type 2 diabetes. Thus, the treatment of diabetes is multidisciplinary. Whenever possible, patients should work with a diabetes-care team and they should always be encouraged to take an active role in managing their disease.

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## SELF-ASSESSMENT

### Physician/ Nurse Practitioner

To receive credit, you must read the monograph and return a completed program evaluation and answer sheet. A test score of 70% or higher is required.

### Physician Assistant

Successful completion of the self-assessment is required to earn Category I (Preapproved) CME credit. Successful completion is defined as commutative score of at least 70% correct.

Your certificate and answer sheet will be mailed 6 to 8 weeks after the receipt of your materials. There is no fee to participate in this activity.

- Under what circumstances should insulin therapy be considered in a patient with type 2 diabetes?**
  - Hyperglycemia >350 mg/dL
  - Ketonuria
  - When glycemic control is inadequate with OADs
  - All of the above
- All of the following statements about PPG are correct EXCEPT \_\_\_\_\_.**
  - High PPG contributes to cardiovascular risk
  - PPG levels contribute substantially to overall glycemic control
  - PPG levels are not important for good glycemic control
  - High PPG contributes to all-cause death
- As patients get closer to achieving target A1C, PPG levels have a(n) \_\_\_\_\_ role in glycemic control relative to FPG.**
  - Lesser
  - Greater
  - Equal
- All of the following are true statements about insulin therapy in type 2 diabetes EXCEPT \_\_\_\_\_.**
  - The risk of hypoglycemia limits the dosage of insulin
  - Insulin analogs have more physiologic time-action profiles compared with human insulin formulations
  - Insulin therapy can be tailored to cover basal and prandial glucose excursions
  - Insulin is rarely required
- Which of the following would be an appropriate initial insulin regimen for a patient with long-standing type 2 diabetes exhibiting nocturia, polyuria, and polyphagia while receiving combination OADs, an A1C of 8.2%, FPG levels averaging 180 mg/dL, and PPG levels averaging 310 mg/dL? The patient has an erratic meal schedule and does not exercise.**
  - A rapid-acting insulin analog
  - A premixed insulin analog formulation before dinner
  - A long-acting insulin analog at bedtime
  - Any of the above
- According to the AACE, what is the goal A1C in type 2 diabetes?**
  - ≤6.0%
  - ≤6.5%
  - <7.0%
  - <8.0%
- All of the following are common concerns for patients starting insulin therapy EXCEPT:**
  - Personal failure
  - Hypoglycemia
  - Weight loss
  - Needle anxiety
- Premixed insulin analogs have the following advantage(s):**
  - Their duration of action is 24 hours
  - They have a more predictable onset of action compared with human insulin
  - They target both PPG and FPG
  - Both b and c
- All the following EXCEPT \_\_\_\_\_ should be considered when adjusting insulin dose.**
  - Age
  - BG
  - Eating patterns
  - Exercise

10. DJ is a 50-year-old female with a BMI of 27.3 in whom type 2 diabetes was diagnosed 10 years ago. She has been using human insulin formulations for nearly 5 years. DJ's blood pressure is 135/85 mm Hg and she also has signs of retinopathy. Although DJ's A1C level has been reduced to 7.6%, she has also experienced wide glucose excursions and nocturnal hypoglycemia. These glycemic problems are most likely related to\_\_\_\_\_.
- Inappropriate insulin regimen
  - Poor control of blood lipids
  - Poor control of hypertension
  - Either a or b
11. Which of the following insulin analogs has no defined peak time of action?
- Insulin lispro
  - Insulin glargine
  - Insulin aspart
  - Premixed formulations
12. All of the following statements are TRUE regarding basal-bolus therapy EXCEPT\_\_\_\_\_.
- It requires multiple daily injections
  - An insulin pump can be used
  - It gives patients more flexibility with mealtimes and lifestyle
  - Carbohydrate counting is not necessary
13. In a patient in whom insulin therapy is being initiated because of increasing A1C values on OADs, what would be the most appropriate starting regimen for covering both FPG and PPG? The patient is anxious about self-injection and wants to do it as conveniently as possible.
- A long-acting insulin analog QD using vial and syringe
  - A rapid-acting insulin analog BID using a pen device
  - A premixed insulin analog formulation BID using a pen device
  - A basal-bolus regimen using an injection device or insulin pump
14. JC is a 50-year-old man with a BMI of 36.5. Although he had maintained good glycemic control on a premixed insulin analog regimen for the past 5 years, recently his BG patterns have become irregular, and A1C has increased from 6.9% 1 year ago to 8.6%. JC has insisted he adheres to his prescribed treatment plan and is very concerned about the loss of control. What regimen change would likely have the most favorable impact on glycemic control?
- A long-acting insulin analog QD using vial and syringe
  - A rapid-acting insulin analog BID using a pen device
  - A premixed insulin analog formulation BID using a pen device
  - A basal-bolus regimen using an injection device or insulin pump

# Insulin Therapy in Type 2 Diabetes: Using Insulin Analogs and Premixed Insulin Analogs (04-SC-04-M-100-NP-PA)

## Program Evaluation and Answer Sheet

Please return this evaluation form and answer sheet for processing/recording of your AMA Category 1 credit for the CME activity.

American Academy of CME, Inc.  
186 Tamarack Circle  
Skillman, NJ 08558

Or fax to: (609) 921-6428

**Please check your professional title:**

- Physician                       Physician Assistant  
 Nurse Practitioner         Other

**Please evaluate or answer the following:**

- |                                                                                      |                              |                             |
|--------------------------------------------------------------------------------------|------------------------------|-----------------------------|
| 1. Did this monograph meet your expectations?                                        | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 2. Was full disclosure, both financial and off-label, made known to the participant? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 3. Was the monograph free of commercial bias?<br>If no, why? _____                   | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

**Please rate the following:**

1=Poor    2 = Fair    3 = Satisfactory    4 = Good    5 = Excellent

- |                                                           |   |   |   |   |   |
|-----------------------------------------------------------|---|---|---|---|---|
| 4. The overall clinical relevance to your practice needs. | 1 | 2 | 3 | 4 | 5 |
|-----------------------------------------------------------|---|---|---|---|---|

### Program Objectives

How well did this program achieve the following objectives?

- |                                                                                                                          |   |   |   |   |   |
|--------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|
| 5. Explain why postprandial glucose excursions need to be controlled in addition to fasting plasma glucose.              | 1 | 2 | 3 | 4 | 5 |
| 6. Give examples of when insulin would be given as initial therapy.                                                      | 1 | 2 | 3 | 4 | 5 |
| 7. Describe two insulin regimens that cover both fasting and postprandial glucose excursions.                            | 1 | 2 | 3 | 4 | 5 |
| 8. Explain how insulin regimens are selected and what factors have to be considered when starting and adjusting insulin. | 1 | 2 | 3 | 4 | 5 |
| 9. Discuss how insulin analogs and premixed insulin analogs provide advantages over human insulin formulations.          | 1 | 2 | 3 | 4 | 5 |
| 10. Describe some common concerns when starting insulin therapy and how these can be overcome.                           | 1 | 2 | 3 | 4 | 5 |
| 11. What one new thing did you learn from this program? _____<br>_____                                                   |   |   |   |   |   |

12. How will you modify your practice as a result of using this program? \_\_\_\_\_  
\_\_\_\_\_

13. What recommendations do you suggest to improve this program? \_\_\_\_\_

\_\_\_\_\_

14. What topics would you like to see in future presentations? \_\_\_\_\_

\_\_\_\_\_

15. How do you obtain CME credit?

(Rate each on a 1 to 5 scale: 1 = Don't use 5 = Strongly Prefer)

Live symposia \_\_\_\_ Print material \_\_\_\_ Web-CME \_\_\_\_ CD-ROM \_\_\_\_ Other \_\_\_\_

Occasionally AACME will be seeking information regarding future needs and outcomes measurements. May we contact you via E-mail for this purpose?  Yes  No

**Note: To receive your CME certificate, you must complete this portion and sign.**

Name (PRINT) \_\_\_\_\_ Degree \_\_\_\_\_

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Time spent on this activity: \_\_\_\_\_ hours \_\_\_\_\_ minutes (required)

(Includes time spent reviewing monograph and completing both the learning assessment and evaluation)

**I CERTIFY THAT I HAVE COMPLETED THIS ACTIVITY AND POST-TEST.**

Signature \_\_\_\_\_

Last four digits of your Social Security number \_\_\_\_\_

## Answer Sheet

Please record your self-assessment answers below by circling the appropriate letter.

- |     |   |   |   |   |
|-----|---|---|---|---|
| 1.  | a | b | c | d |
| 2.  | a | b | c | d |
| 3.  | a | b | c |   |
| 4.  | a | b | c | d |
| 5.  | a | b | c | d |
| 6.  | a | b | c | d |
| 7.  | a | b | c | d |
| 8.  | a | b | c | d |
| 9.  | a | b | c | d |
| 10. | a | b | c | d |
| 11. | a | b | c | d |
| 12. | a | b | c | d |
| 13. | a | b | c | d |
| 14. | a | b | c | d |



