

## 2007 Diabetes Update: Using Insulin Effectively

### What We Know About Diabetes

- Type 2 diabetes is the most common form of diabetes
- Residual insulin production progressively lessens in type 2 diabetes as pancreatic beta-cell function declines
- Good glycemic control decreases the risk of microvascular and macrovascular complications from diabetes

### Learning Objectives

After completing this activity, participants should be better able to:

- State current management goals for diabetes
- Identify barriers to optimal use of insulin and how to overcome them
- Discuss the roles of short-, intermediate-, and long-acting insulins in the management of diabetes

**Evidence suggests that clinicians wait too long before intensifying treatment and adding insulin**

### Diabetes: A Growing Concern

**D** diabetes affects an estimated 21 million people in the United States,<sup>1</sup> and its prevalence is increasing. In the decade between 1990-1994 and 2001-2004, physician-diagnosed diabetes increased by 30% to 50% among most demographic groups, with the highest percentage in the Mexican and black populations (Table 1).<sup>2</sup> In any given clinician's practice, 1 of 10 adult patients and approximately 1 of 5 older adults has diabetes.<sup>2</sup> However, diabetes is undiagnosed in nearly one third (6.2 million persons) of the US population.<sup>2</sup>

Type 2 diabetes is the most common form of diabetes, accounting for 90% to 95% of all cases of diabetes worldwide.<sup>1</sup> Patients with type 2 diabetes maintain a residual degree of insulin production that progressively lessens with time as pancreatic beta cells continue to

**How do patients who don't have regular meal-times control their glucose?**

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lose function. Unlike type 1 diabetes, which is an autoimmune disease, type 2 diabetes is acquired and highly associated with older age, physical inactivity, and obesity.<sup>1</sup> The incidence of type 2 diabetes has been increasing in younger persons because of the obesity epidemic among children and adolescents.<sup>1</sup>

### Glycemic Control Is Critical to Prevent Complications

Hyperglycemia, the cardinal symptom of diabetes, leads to microvascular (retinopathy, nephropathy), macrovascular (myocardial infarction [MI], stroke), and neuropathic complications and is associated with increased mortality.<sup>3</sup> The A1C fraction of glycosylated hemoglobin (A1C) in the blood is used to judge glycemic control in patients with diabetes. An A1C level <6% is considered normoglycemic. The target A1C levels considered optimal by the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and the European Association for the

Study of Diabetes (EASD) are listed in Table 2.<sup>4,5</sup> (For a discussion of the role of A1C in diagnosing diabetes, see *Can A1C Testing Accurately Diagnose Diabetes?* on page 3.)

The United Kingdom Prospective Diabetes Study (UKPDS), an observational study of 5102 patients with type 2 diabetes, showed that reducing the A1C level decreases the risk of microvascular and macrovascular complications (Figure 1).<sup>3</sup> Each 1% reduction in A1C level

#### Diabetes Demographics in the United States

##### Population Aged ≥20 Years

	Physician-Diagnosed Diabetes (%)		Undiagnosed Diabetes (%)	
	1990-1994	2001-2004	1990-1994	2001-2004
Male	5.4	7.6	3.5	4.3
Female	5.4	7.1	2.6	1.8
White	5.0	6.2	2.6	2.8
Black	8.6	11.4	4.2	3.1
Mexican	9.7	11.8	4.7	3.3
Total	5.4	7.3	3.0	3.0

Adapted from National Center for Health Statistics.<sup>2</sup>

#### Suggested A1C Targets

Optimal target: A1C <6% (normal range)

Organization	A1C Target (%)
AACE	<6.5
EASD	<6.5
ADA	<7 (general) <6* (individual patient)

\*As close to normal (<6%) without significant hypoglycemia.

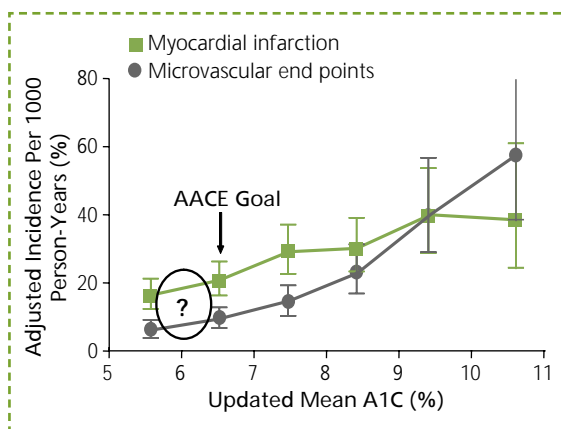


Figure 1. Incidence of CV events in patients with diabetes (UKPDS). Stratton IM et al.<sup>3</sup>

## Can A1C Testing Accurately Diagnose Diabetes?

Although the ADA recommends A1C testing for monitoring glycemic control in patients with known diabetes, it does not advocate using A1C levels for diagnosis. Instead, it recommends FPG measurement (a level  $\geq 126$  mg/dL is diagnostic) as the preferred diagnostic test for diabetes because of the test's ease of use, lower cost compared with other screening tests, and patient acceptance.<sup>1</sup> Some clinicians and researchers have argued for the diagnostic utility of A1C measurement.<sup>2-6</sup> Use of A1C testing has been proposed as an alternative to FPG testing<sup>4</sup> or as a diagnostic tool in combination with measurement of fasting or random plasma glucose levels.<sup>4-6</sup> In addition, European guidelines have included A1C

measurement (with confirmatory glucose measurements) among the recommended diagnostic tests for diabetes.<sup>7</sup>

Current objections to A1C testing for diagnosing diabetes center on the imperfect correlation between A1C and FPG levels.<sup>5</sup> Although an elevated A1C level is highly specific for diagnosing diabetes, its sensitivity can be low, depending on the cut-off value (see Table).<sup>4</sup> Some clinicians believe that A1C testing, despite its low sensitivity, may be useful for identifying diabetes cases requiring pharmacologic intervention because aggressive treatment often is not initiated until A1C levels are  $\geq 7.0\%$ .<sup>2</sup> An analysis of FPG, oral glucose tolerance test (OGTT), and A1C data from 244 patients screened for participation in the Early Diabetes Intervention program found that A1C measurement significantly improved the sensitivity of diabetes screening in high-risk patients. Among 101 patients with OGTT-diagnosed diabetes, A1C testing (criteria: levels  $> 2$  standard deviations above the mean) identified 62 (61%) patients with diabetes compared with 45 (45%) identified by FPG testing (criteria: levels  $\geq 126$  mg/dL) ( $P = .002$ ).<sup>8</sup>

**Table.**  
Sensitivity and Specificity of A1C Testing for Diagnosing Diabetes\*

A1C Cut-Off Value (%)	SDs Above Mean	Sensitivity (%)	Specificity (%)
5.6	1	83.4	84.4
6.1	2	63.2	97.4
6.5	3	42.8	99.6
7.0	4	28.3	99.9

\*Defined as FPG  $\geq 126$  mg/dL. SD = standard deviation. Rohlifing CL et al.<sup>4</sup>

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was associated with risk reductions of 37% for microvascular complications, 14% for MI, 43% for peripheral arterial disease (PAD), 21% for diabetes-related mortality, and 21% for any diabetes-related end point (all,  $P < .0001$ ).<sup>3</sup> In addition, there were significant reductions in fatal and nonfatal stroke (12%;  $P = .035$ ) and heart failure (16%;  $P = .016$ ).<sup>3</sup>

There was no threshold level beyond which additional reductions in A1C produced no benefit.<sup>3</sup> Thus, patients with A1C levels in the range of 6.2% to 6.5%, for example, may benefit from aggressive therapy. In UKPDS, patients who received intensive treatment had significantly lower risk for microvascular complications than patients who received conventional treatment ( $P = .0099$ ), with a trend toward lower risk for MI as well ( $P = .052$ ).<sup>3</sup>

The AACE estimates that only 33% of Americans with diabetes meet the target A1C level.<sup>6</sup> In addition, data from the National Health and Nutrition Examination Survey (NHANES) show an overall decline in the percentage of patients with A1C levels  $< 7\%$ , from 44.3% in the NHANES III (1988-1994) report to 37.0% in 1999-2000.<sup>7</sup>

## Achieving Glycemic Control Can Be Challenging

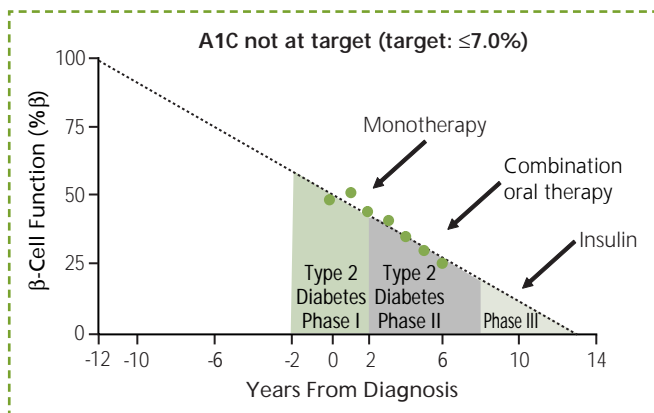
### *Diabetes Is Progressive*

The progressive nature of type 2 diabetes complicates efforts to maintain lower A1C levels. Patients with type 2 diabetes often are not diagnosed until complications occur. Some patients with diabetes may be undiagnosed for as long as 9 to 12 years.<sup>8</sup> In addition, despite all forms of treatment, beta-cell function continues to deteriorate.

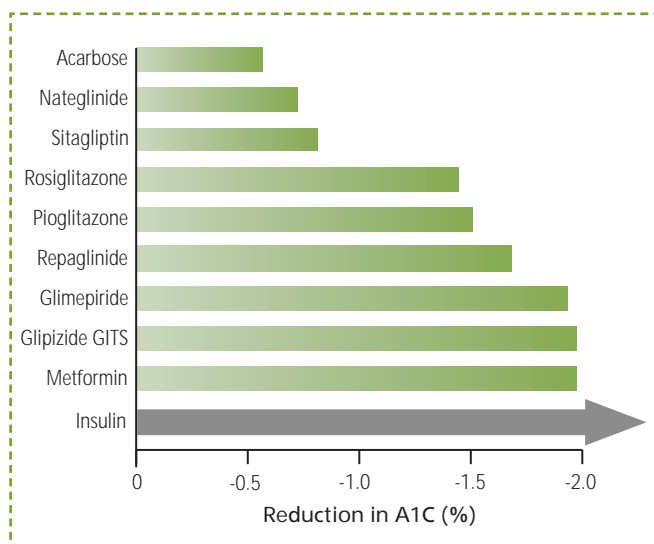
In UKPDS, beta-cell function declined significantly ( $P < .0001$ ) from baseline to year 6 in all patients, regardless of whether conventional or intensive treatment was used (Figure 2).<sup>9</sup> Patients who had intensive treatment reduced their median A1C level to 6.1% (from 6.9% at baseline) after 1 year,<sup>9</sup> but the A1C levels rose to 7.1% by year 6 of the study despite therapy and dose increases.<sup>9</sup> Patients who received only dietary therapy fared worse, experiencing a continued decline in beta-cell function, with function at year 6 barely half that at baseline.<sup>9</sup>

### *Oral Therapy: A Key But Limited Role*

Oral antidiabetic drugs (OADs) play a key role in the treatment of type 2 diabetes. For most patients, a single OAD combined with diet and lifestyle modifications can effectively



**Figure 2.** Beta-cell function continues to decline in type 2 diabetes, necessitating more intensive therapy over time. UKPDS 16.<sup>9</sup>



**Figure 3.**

**Antiglycemic effects of OADs compared with insulin.**

The antiglycemic effect varies among OADs and is highest with metformin and the sulfonylureas. Aronoff S et al. *Diabetes Care*. 2000;23:1605-1611; Garber AJ et al. *Am J Med*. 1997;102:491-497; Goldberg RB et al. *Diabetes Care*. 1996;19:849-856; Hanefeld M et al. *Diabetes Care*. 2000;23:202-207; Lebovitz HE et al. *J Clin Endocrinol Metab*. 2001;86:280-288; Simonson DC et al. *Diabetes Care*. 1997;20:597-606; Wolfenbuttel BH et al. *Drugs*. 1995;50:263-288; Precose (acarbose). Prescribing information. West Haven, Conn: Bayer; 2003.

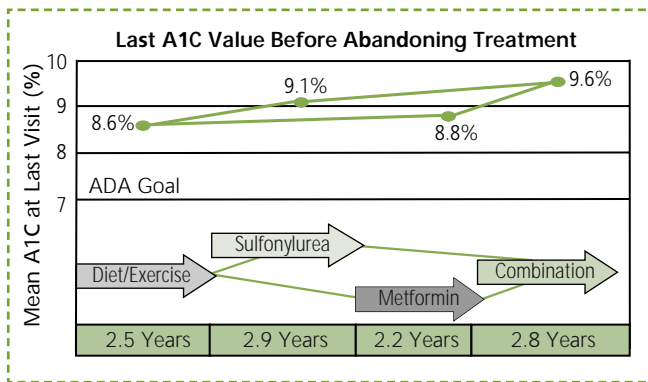
control fasting plasma glucose (FPG) and A1C for several years after diagnosis. At that point, treatment must be intensified conventionally with the addition of a second OAD. This regimen may maintain glycemic control for another few years. By year 5 or 6 postdiagnosis, most patients with type 2 diabetes require additional therapy to maintain the tight glycemic control necessary to avoid complications.<sup>10</sup>

Current guidelines for treating hyperglycemia recommend lifestyle intervention plus metformin as the first step in therapy, with A1C assessment at 3 months.<sup>11</sup> The expected decrease in A1C with lifestyle and dietary modifications is 1% to 2% and approximately 1.5% with metformin.<sup>11</sup> For mechanistic reasons, the decrease in A1C resulting from OADs is limited (Figure 3). Metformin and the secretagogues appear to decrease the A1C level the most. When choosing an OAD for patients, practitioners should be aware of what degree of improvement can be expected with each OAD.

### ***Insulin Therapy Often Is Delayed Too Long***

There is no cap on the decrease in A1C level achievable with insulin. Insulin will lower A1C infinitely, limited only by hypoglycemia. However, for many patients, insulin alone does not achieve A1C goals. In UKPDS, patients treated with insulin plus continued OAD therapy achieved the lowest A1C levels and maintained those levels for the longest period of time.<sup>10</sup>

Evidence suggests that in clinical practice, clinicians wait too long before intensifying treatment and adding insulin. Allowing A1C levels to remain unacceptably high puts patients at additional risk for hyperglycemia-associated complications. Almost 6 years may elapse with A1C levels >7% before OAD therapy is initiated, and average A1C levels reach 9.6% before combination therapy is started (Figure 4).<sup>12</sup> Patients with type 2 diabetes may have the disease for 10 to 15 years before insulin therapy is initiated. By that time, microvascular and cardiovascular (CV) complications associated with hyperglycemia become clinically evident.<sup>13</sup>



**Figure 4.** Failure to advance therapy when required. Clinical inertia occurs when treatment is not intensified as necessary to avoid the complications associated with hyperglycemia. Brown JB et al.<sup>12</sup>

### Barriers to Initiating Insulin Therapy

A 2005 survey of diabetes educators found that patient resistance to starting insulin was based on several factors, including fear of the pain associated with injections and complications, concern about weight gain, time involved, inconvenience, inadequate support or resources, lack of updated information, and physician resistance to insulin therapy.<sup>14</sup>

### Patients' Misperceptions About Insulin Therapy

Despite the efforts of practitioners and diabetes educators, patients with diabetes have misperceptions about insulin therapy (Table 3). Many patients believe that insulin is required because they have not been compliant with OAD therapy. In 1 survey, 58% of patients expressed the belief that insulin therapy was a sign they had failed therapy or that insulin was a "punishment."<sup>14,15</sup> Practitioners must help patients understand that the addition of insulin does not suggest that previous treatments were inadequate or improperly used. It is the inexorable decline in beta-cell function, as demonstrated by UKPDS,<sup>10</sup>

that mandates the intensification of therapy to maintain good glyceemic control.

A second barrier is fear of injection. Patients often are unfamiliar with current insulin injectors, which use silicon-coated, microfine needles instead of the needles and syringes used in the past. Needle use also carries a negative image in society, perhaps because of an association with illegal drug use.<sup>10</sup> Patients should be reassured that most insulin injections are painless and that needles are incapable

Patient Barriers to Insulin Use: Perception vs Reality

Perception	Reality
<b>Failing oral therapy</b>	
58% of patients believe using insulin means they have failed OAD therapy	OAD failure is due to progressive nature of type 2 diabetes; insulin is best agent to control disease
<b>Needle phobia</b>	
Fear associated with early experiences	Current needles considered painless; easy-to-use injection systems are available
<b>Fear of complications</b>	
Common association of insulin with diabetic complications	Complications are due to uncontrolled, progressive disease; insulin actually results in reduction of vascular damage

Meece J14; Peyrot M et al.<sup>15</sup>

of puncturing arteries or veins. The availability of pen-type injectors as an alternative should facilitate insulin use.

A third misperception is that insulin therapy causes complications. In reality, the complications result from poor glycemic control. Good patient education must clarify that insulin therapy is not the cause of such complications, but instead is the best therapy available to control hyperglycemia and *prevent* complications.

### ***Clinicians' Misperceptions About Insulin Therapy***

Clinicians can be a barrier to insulin therapy (Table 4).<sup>16</sup> In 1 study, one third of physicians surveyed said they hold back insulin until “absolutely necessary” and view it as a treatment of last resort.<sup>14</sup>

A common misperception among clinicians is that insulin therapy is highly associated with hypoglycemia. Hypoglycemia is common in type 1 diabetes and less common in type 2 diabetes, the form of the disease seen most often in clinical practice,

because some residual insulin function remains to help stabilize glucose control. The UK Hypoglycemia Group study reported that severe hypoglycemia occurred at a rate of only 2 episodes per 100 patient years in patients with type 2 diabetes treated with insulin.<sup>17</sup>

Clinicians also fear that insulin may increase the risk of atherosclerosis. However, there is no evidence that insulin used clinically exacerbates CV disease, while several studies suggest it improves outcome. In one study comparing insulin with sulfonylurea, insulin treatment significantly improved lipid profiles independent of glycemic control.<sup>18</sup> In addition, intensive insulin therapy after MI has increased long-term survival in patients with diabetes.<sup>19,20</sup>

Weight gain is another concern with insulin therapy. Except for metformin, most pharmacologic interventions that improve metabolic control in patients with diabetes are associated with weight gain.<sup>13</sup> However, proper counseling, diabetes nutrition education, and careful consideration of combination therapy help to minimize weight gain. For example, combining insulin with metformin results in better glycemic control, less weight gain, and a lower total insulin requirement than insulin monotherapy.<sup>21</sup>

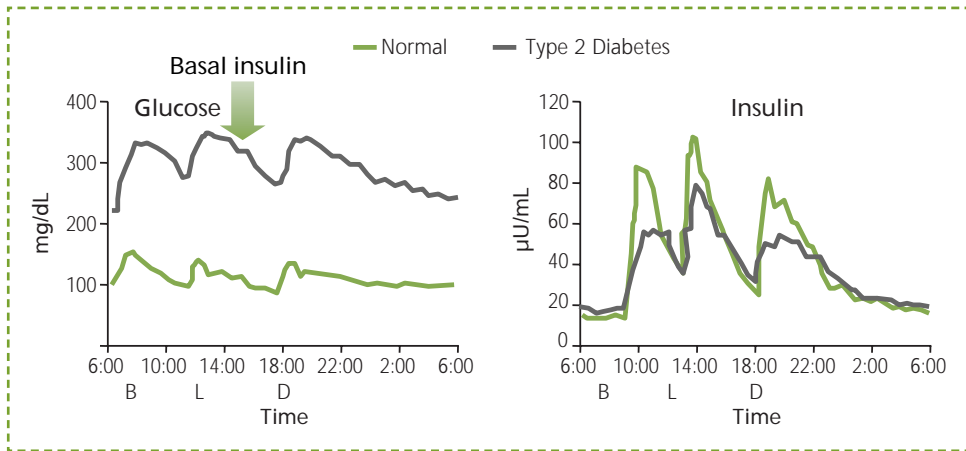
Clinicians need to adjust their own thoughts to reflect current reality and project a positive attitude to their patients about the use of insulin. Clinicians who have a negative attitude about insulin impart that attitude to their patients. Clinicians must also educate their patients about the progressive nature of diabetes and reassure them that insulin is not a punishment but rather a very effective therapy for controlling diabetes and preventing complications.

**Clinician Barriers to Insulin Use: Perception vs Reality**

Perception	Reality
Hypoglycemia is prevalent with insulin use	Severe hypoglycemia is uncommon in patients with type 2 diabetes, occurring at 10% the rate in patients with type 1 diabetes
Insulin use increases atherosclerosis	Studies indicate no exacerbation of cardiovascular disease
There is weight gain with insulin use	Weight gain is modest and can be controlled with diet and exercise
Patients have a negative attitude regarding insulin use	Insulin is a “positive” approach to achieving glycemic control

Doek IF et al<sup>21</sup>; Malmberg K et al<sup>19,20</sup>; Romano G et al<sup>18</sup>; UKPDS Group.<sup>16</sup>

TABLE 4



**Figure 5.** The aim of basal insulin therapy is to mimic normal glucose and insulin rhythms. Patients with type 2 diabetes have elevated glucose levels throughout the day and secrete less insulin in response to meals than normoglycemic persons. B = breakfast; D = dinner; L = lunch. Polonsky KS et al.<sup>22</sup>

### Options for Initiating Insulin Therapy

#### Basal insulin

- ➔ NPH insulin (at bedtime)
- ➔ Insulin detemir (once or twice daily)
- ➔ Insulin glargine (once daily)

#### Premixed insulin preparations

- ➔ 70/30 NPH insulin/regular insulin
  - ➔ 50/50 NPL insulin/insulin lispro
  - ➔ 70/30 NPA insulin/insulin aspart
  - ➔ 75/25 NPL insulin/insulin lispro
- } Analog premixes

NPA = neutral protamine aspart;  
NPL = neutral protamine lispro.

### When A1C Goals Are Not Achieved With OADs: Management Strategies

Even early in treatment, not all patients can successfully achieve target A1C goals with 1 or more OADs. The ADA recommends 3 possible strategies for managing type 2 diabetes when A1C levels remain >7% despite maximally tolerated doses of metformin plus lifestyle modification: (1) add basal insulin, considered most effective; (2) add a sulfonylurea, considered least expensive; or (3) add a glitazone, which offers the advantage of no hypoglycemia.<sup>11</sup> Basal insulin is the preferred choice for patients with A1C levels >8.5% because it is more likely to achieve target goals.<sup>11</sup> Current thinking is that intensifying therapy by adding a third OAD is less effective and more expensive than initiating insulin.<sup>11</sup>

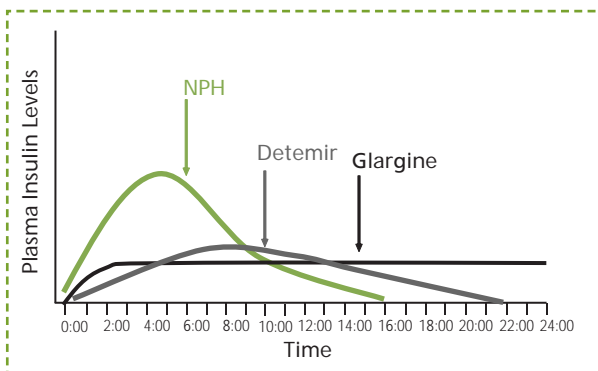
### Using Basal Insulin Therapy

Basal insulin refers to the long-acting form of insulin, which provides a background insulin level throughout the day. In persons without diabetes, about half of the insulin produced during the day is long-lasting basal insulin and about half is prandial insulin, which peaks at meal times (Figure 5). Patients with diabetes secrete less prandial insulin after meals, particularly after the main meal; have higher glucose levels at the start of the day and at mealtimes; and secrete 70% less insulin during induced hyperglycemia than persons without the disease.<sup>22</sup> The rationale for basal insulin

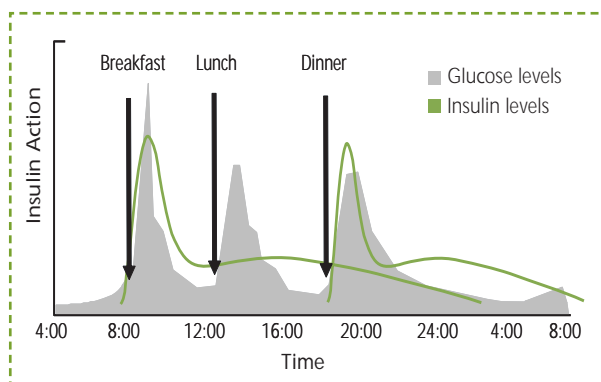
therapy is to supply insulin over 24 hours and control the morning FPG to a target level of 100 to 110 mg/dL. The dose of basal insulin is titrated upward until that FPG goal is met.

There are several forms of basal insulin (Table 5). Glargine and detemir are insulin analogs, recombinant human insulin products that are similar to human insulin except for changes in the isoelectric point (glargine) or acetylation of the insulin molecule (detemir).<sup>23</sup> Both have a long duration of action. Glargine provides a constant level of insulin for at least 24 hours,<sup>24</sup> while detemir has a slightly more bell-shaped distribution and a duration of action slightly less than 24 hours (Figure 6),<sup>23</sup> which may necessitate twice-daily dosing for some patients.<sup>24</sup> Neutral protamine Hagedorn (NPH), an older insulin, is not as physiologic as glargine and detemir and has an intermediate duration of action. Its action peaks about 4 to 6 hours after administration with a total duration of action of 12 to 16 hours.<sup>24</sup>

Premixed insulin formulations are administered prior to a meal, usually the evening meal for once-daily administration, to offset the increase in glucose that follows ingestion of food. After the initial insulin spike, which is necessary to control postprandial glucose (PPG), insulin levels continue to be elevated for an extended time (Figure 7). This is a concern because insulin levels that are elevated overnight, when insulin is not needed, may result in hypoglycemia.



**Figure 6.** Hypothetical profiles of human insulin and basal insulin analogs. NPH, an intermediate-acting insulin, has a higher and earlier peak with shorter duration of action than the long-acting insulin analogs detemir and glargine. Detemir has a shorter duration of action than glargine, necessitating twice-daily dosing for some patients. Plank JJ et al<sup>23</sup>; Rosenstock J et al<sup>24</sup>; Rave K et al. *Diabetes Care*. 2005;28:1077-1082.



**Figure 7.** Profile of twice-daily premixed insulin analogs (lispro 75/25 or aspart 70/30). Premixed insulin analogs usually are dosed before the evening and morning meals. They provide a peak of prandial insulin to control PPG and a longer-lasting insulin level that is similar to basal insulin. As the figure shows, no prandial insulin response accompanies lunch. A concern with premixed insulin analogs is the overnight level of insulin (24:00 to 8:00), which can lead to hypoglycemia. Nathan DM<sup>13</sup>; Leahy J. In: Leahy J et al, eds. *Insulin Therapy*. New York, NY: Marcel Dekker; 2002:87-112.

### ***Considering GLP-1 Agents***

Digestive hormones known as *incretins* affect the body's insulin response to glucose challenge.<sup>25</sup> Glucagon-like peptide (GLP)-1, an incretin hormone, boosts insulin production, suppresses glucagon secretion, slows the rate of gastric emptying, and promotes satiety.<sup>26,27</sup> Because patients with diabetes have decreased levels of GLP-1 and inadequate GLP-1 responses, GLP-1 has attracted clinical interest as a therapeutic target.

As a therapeutic agent, natural GLP-1 is problematic because it is degraded quickly by dipeptidyl peptidase (DPP)-IV and has a half-life of 1 to 2 minutes.<sup>26</sup> Two approaches to enhancing GLP-1 function have been investigated and approved for use in treating diabetes: incretin mimetics and DPP-IV inhibitors. The incretin mimetics (exenatide, liraglutide) are injected subcutaneously and act similarly to GLP-1 but are resistant to DPP-IV degradation. The result is a longer duration of action that allows once- or twice-daily administration.<sup>27</sup> The DPP-IV inhibitors (sitagliptin, vildagliptin) are oral agents that slow the inactivation of GLP-1 by blocking the actions of DPP-IV.<sup>27</sup>

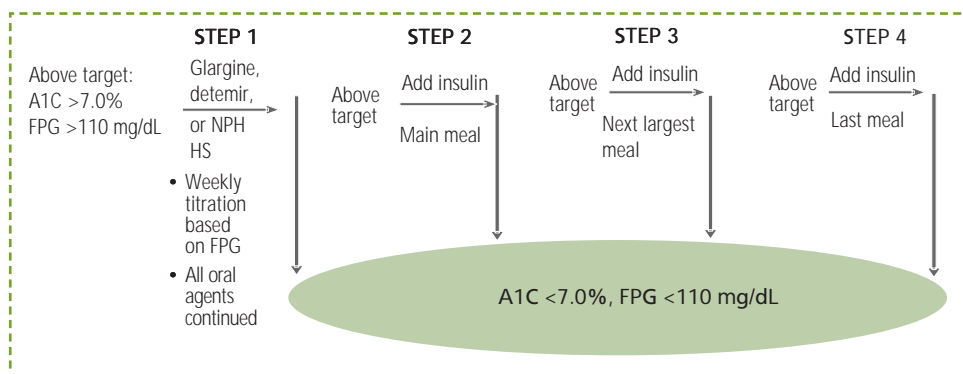
GLP-1 agents offer another treatment option for patients whose A1C levels are not controlled by OAD therapy. In a noninferiority trial, exenatide resulted in A1C reductions similar to biphasic insulin aspart and provided better glycemic control.<sup>28</sup> Exenatide (10 µg bid, administered before breakfast and the evening meal) and glargine (average dose at week 26, 25 U/d, administered at bedtime) are equally effective in improving glycemic control when added to OAD therapy in patients with a mean baseline A1C of 8.2% or 8.3%, respectively.<sup>26</sup> Glargine more effectively controls FPG and exenatide more effectively controls peak PPG.<sup>26</sup> Patients treated with exenatide lost weight (mean decrease, 2.3 kg) over 26 weeks of treatment, while those treated with glargine gained weight (mean increase, 1.8 kg).<sup>26</sup> Patients treated with exenatide experienced significantly more gastrointestinal side effects, which is the main factor limiting the use of this agent. Insulin glargine and exenatide were equally effective in reducing A1C levels by 1.2 % to the 7.0% goal. This is the usual maximum effect of exenatide. Higher baseline A1C levels would probably require insulin to achieve goal.

### ***Transitioning From Basal to Basal-Bolus Insulin***

Figure 8 illustrates steps a clinician might take for a patient who presents with levels of A1C >7% and FPG >110 mg/dL.<sup>11,29</sup> Consideration should be given first to adding a basal insulin to the existing OAD regimen.<sup>11</sup> Premixed insulins are not recommended for the dose-adjustment stage of insulin therapy, but can be used once insulin doses have stabilized.<sup>11</sup> Insulin doses are titrated weekly to achieve target FPG levels.

If the FPG remains above the target level, ongoing dose increases in basal insulin are recommended. If, however, FPG is controlled, but A1C is still above target after about 3 months' treatment, adding a rapid-acting prandial insulin with the day's main meal is the probable next step. Adding this agent before or after the main meal should help patients achieve the A1C goal.

Finally, if FPG remains <110 mg/dL but A1C levels are still >7%, additional doses of prandial insulin can be added, first after breakfast and finally after the midday meal, to better control PPG excursions and help achieve glycemic control.



**Figure 8. Steps in transition from basal to basal-bolus insulin therapy in type 2 diabetes.** In step 1, add a basal insulin to the existing OAD regimen. In step 2, increase basal insulin dose, but if FPG is controlled while A1C is still above goal after 3 months, give a rapid-acting prandial insulin before the main meal. In step 3, add further prandial insulin if FPG is controlled but A1C remains >7%. In step 4, intensify measures taken in step 3 to control PPG excursions and achieve glycemic control. HS = at bedtime. Karl DM.<sup>29</sup>

## Summary

Intensive control of hyperglycemia can lower the risk of serious and debilitating complications of type 2 diabetes and diabetes-associated mortality. Too often, however, clinicians postpone initiation of insulin therapy and instead supplement metformin therapy with additional OADs. The ADA recommends insulin as the most effective means of achieving glycemic control when patients are poorly controlled on high-dose metformin, and initiation of insulin is a reasonable early step in the management of type 2 diabetes. Insulin therapy can be initiated with a long-acting basal insulin analog and intensified with a rapid-acting insulin analog when further control of PPG is necessary. Clinicians should approach insulin therapy with a positive attitude and ensure that patients understand that insulin is not a punishment and is not associated with complications. It is the most potent method available for achieving glycemic control, and eventually a necessary step for most people with type 2 diabetes. Delaying insulin therapy because of misperceptions or fears places patients at higher risk for complications and should be avoided.

## CASE STUDY

### A 60-Year-Old Man With 10-Year History of Type 2 Diabetes and Hypertension

#### Presentation

This patient's current diabetes treatment regimen includes metformin 1000 mg bid, rosiglitazone 8 mg in the morning, and glimepiride 8 mg qd, but he has not achieved glycemic control. He also takes numerous medications for comorbidities.

- Hypertension: lisinopril 40 mg, amlodipine 10 mg, hydrochlorothiazide 12.5 mg
- Dyslipidemia: atorvastatin 10 mg

Physical examination reveals problems with weight and borderline hypertension despite treatment.

#### Physical Examination

- Weight: 245 lb (10-lb increase since last visit)
- Height: 6 ft 0 in
- Body mass index: 34.2 kg/m<sup>2</sup>
- Waist circumference: 44 in
- Blood pressure: 130/80 mm Hg

#### Laboratory Results

- Lipids
  - Total cholesterol: 167 mg/dL
  - Triglycerides: 206 mg/dL
  - HDL: 35 mg/dL
  - LDL: 90 mg/dL
- A1C: 8.9%
- Plasma glucose in office: 196 mg/dL
- Creatinine: 1.1 mg/dL
- Hepatic function: normal

The patient is very concerned that he has failed treatment because he is unable to achieve glycemic control with the OADs. The clinician reassures him that the progressive nature of diabetes is responsible for the hyperglycemia, not that he used his treatments improperly, and explains that 6 to 10 years after diagnosis, OADs alone are unable to control hyperglycemia in most patients with type 2 diabetes. The clinician tells the patient that he is likely to benefit from the addition of insulin to his diabetes treatment regimen. The clinician presents a positive attitude about adding insulin, and this helps the patient overcome his fear of and negative attitude toward insulin. The patient is encouraged to be part of a team

with the clinician in tackling hyperglycemia and learning to administer and titrate his insulin. He agrees to basal insulin therapy.

#### Clinical Decision Point

*Which insulin should be used and at what dose?*

- NPH at bedtime
- Once-daily glargine
- Twice-daily premixed insulin
- Detemir at bedtime

#### Comment

During initiation of insulin therapy, a period of titration or dose adjustment is expected. As the ADA recommends against using a pre-mixed insulin during this phase of treatment, the choice is NPH insulin or long-acting insulin analogs (glargine and detemir). Glargine is an attractive choice because it requires once-daily administration and provides a steady level of insulin throughout the day (Figure 6, page 9).

The accepted starting dose for insulin when added to ongoing OAD therapy is 10 U/d, which is then titrated according to morning FPG levels. Table 6 shows the simple titration algorithm used in the Treat-to-Target trial, which adjusts the insulin dose on a weekly basis.<sup>30</sup> This algorithm is based on patients' self-monitored blood glucose (SMBG) measurements averaged over the previous 7 days. Depending on the result, the insulin dose is increased in increments of 2 U/d, which is why it is called the *2-4-6-8 titration algorithm*. It is effective at achieving

**Table 6.**  
**2-4-6-8 Insulin Titration Algorithm\***

- Patients (n = 756) with inadequate glycemic control (A1C >7.5%) taking 1 or 2 oral agents
- Started with 10 U/d bedtime basal insulin and adjusted weekly to target FPG ≤100 mg/dL

Mean Self-Monitored FPG Values From Preceding 2 Days (mg/dL)	Increase of Insulin Dosage (U/d)
≥180	8
140-180	6
120-140	4
100-120	2

\*From the Treat-to-Target trial. Riddle MC et al<sup>30</sup>; Hermansen K et al.<sup>32</sup>

control without causing hypoglycemia. An alternative algorithm is to adjust the basal insulin dose upward by 2 U every 3 days until FPG ≤100 mg/dL is achieved.<sup>31</sup>

Patients in the Treat-to-Target trial had poor glycemic control taking ≥1 OAD (>70% were taking 2 OADs)<sup>30</sup>; glargine or NPH insulin was injected at bedtime.<sup>30</sup> The degree of glycemic control achieved with glargine and NPH insulin was similar after 24 weeks of treatment, with FPGs at 117 mg/dL and 120 mg/dL, respectively, and A1C levels of 6.96% and 6.97%, respectively.<sup>30</sup> With insulin treatment, FPG was normalized in only 12 to 16 weeks and A1C in about 16 weeks. Subsequent studies have shown equal efficacy when glargine is injected either in the morning or at bedtime.

Glargine treatment had a lower risk of hypoglycemia compared with NPH. Patients treated with glargine had 3.0 confirmed events of hypoglycemia (≤56 mg/dL) per patient-year compared with 5.1 in patients treated with NPH, a significant difference ( $P < .003$ ).<sup>30</sup> Glargine, which has a more physiologic profile than NPH, was particularly effective for averting hypoglycemic episodes during the late night/early morning hours. More patients treated with glargine than with NPH reached the A1C target goal (33.2% vs 26.7%, respectively;  $P < .05$ ) and FPG goal of ≤100 mg/dL (22.1% vs

15.9%, respectively;  $P < .03$ ) without episodes of nocturnal hypoglycemia.<sup>30</sup>

Similar findings were seen in a study comparing twice-daily detemir with twice-daily NPH in insulin-naïve patients who were poorly controlled with OADs.<sup>32</sup> At 24 weeks, glycemic control was similar in both groups, with A1C reductions of 1.8% and 1.9% in the detemir and NPH groups, respectively.<sup>32</sup> Detemir produced fewer episodes of hypoglycemia and was associated with a 55% lower risk for nocturnal hypoglycemia than NPH ( $P < .001$ ).<sup>32</sup>

### 1-Month Follow-Up Visit

The patient is started on 10 U/d of glargine and instructed to titrate according to the 2-4-6-8 algorithm, with the goal of achieving an FPG between 100 and 110 mg/dL. He is asked to return in 1 month for an assessment. At that time, the patient reports using up to 30 U/d of insulin, but his FPG is still >200 mg/dL. He is very frustrated and expresses the feeling that the “insulin doesn’t work.”

### Clinical Decision Point

#### What is the best next step?

- Continue to increase the insulin dose
- Switch to twice-daily premixed insulin
- Switch to exenatide
- Refer the patient for a consultation on gastric bypass

### Comment

The lower risk of hypoglycemia with glargine and detemir makes an increase in the insulin dose an option that would be less attractive if the patient were using NPH insulin. Many clinicians are hesitant to increase the insulin dose beyond 30 U, but there is no physiologic reason why the insulin dose cannot be increased to the point where control is achieved with minimal risk of hypoglycemia. In the Treat-to-Target trial, the mean daily dose of glargine was 47 (±1.3) U/d and of NPH, 42 (±1.3) U/d.<sup>30</sup> As long as FPG is >100 to 110 mg/dL, the risk of hypoglycemia remains low. About 50% to 60% of a patient’s weight is used to determine the insulin dose; for example, a

**CASE STUDY** (continued)

100-kg man may require as much as 50 to 60 U/d of basal insulin. Patients with severe insulin resistance may require very high doses.

**4-Month Follow-Up Visit**

The patient titrated his insulin to meet FPG goals and is using 75 U/d of glargine. His FPG is well controlled and usually <100 mg/dL. At the last visit, A1C was 6.9%, and he was told to monitor his PPG levels on occasion. He reports that the insulin injections are painless, and he feels like a partner in maintaining his own health and well-being.

**3-Year Follow-Up Visit**

The patient maintains control after starting insulin and is routinely seen every 3 to 4 months over the next 3 years. During that time he remains medically stable and his A1C levels stay between 6.5% and 7.2%. At his next visit, however, his A1C level has increased to 8.2%, although he continues to maintain good control of his FPG.

**Clinical Decision Point**

*What is the best next step for this patient's treatment?*

- ➔ Increase glargine dose
- ➔ Switch to twice-daily premixed insulin
- ➔ Switch to 4-injection basal-bolus regimen
- ➔ Increase self-monitored glucose testing to before meals and before bedtime

**Comment**

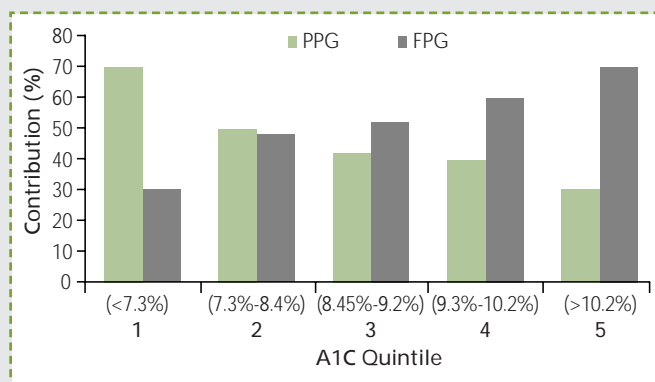
When a patient's FPG level is well controlled but A1C remains above target, sub-optimal control of PPG is suggested. Increasing the basal insulin dose while the patient's FPG level is normal risks producing hypoglycemia. The next target of therapy should be to control PPG excursions.

Glycemic control as measured by A1C has 2 components: FPG and PPG. At A1C levels between 7.3% and 8.4%, these components contribute equally. As A1C levels increase, however, FPG plays a larger role than PPG. The opposite is true as A1C levels decrease (Figure 9),<sup>33</sup> requiring better PPG control to continue to achieve the A1C target.

Both premixed insulin and basal-bolus regimens target PPG by supplying rapid-acting insulin that helps control the glucose released following a meal. The body releases insulin in response to the glucose introduced with each meal; for patients with type 2 diabetes, this insulin release is particularly weak after the main meal when endogenous insulin is exhausted (Figure 10). Basal insulin and premixed insulin provide similar PPG control earlier in the day, but at the evening meal, PPG control with premixed insulin tends to be better (Figure 10).<sup>34</sup>

**Follow-Up Visit 3 Months Later**

The patient was switched to a premixed insulin (40 mg bid) and referred to a diabetes educator to reinforce instructions on lifestyle modification, diet, and blood glucose monitoring. At his 3-month routine follow-up visit, he reports that he had some



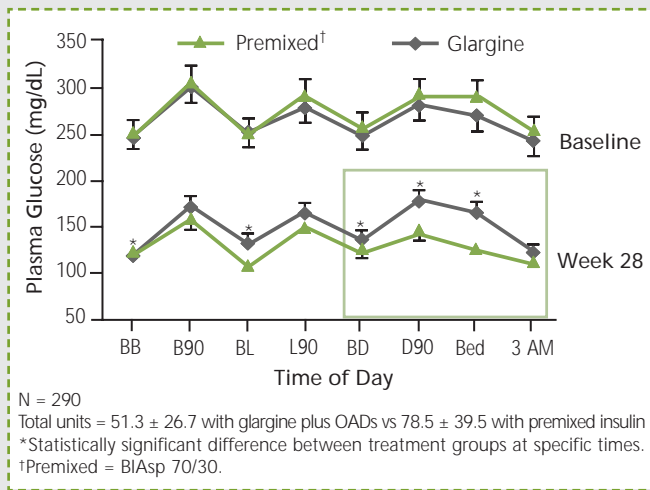
**Figure 9.** At lower A1C levels, PPG plays a proportionally more important role than FPG in glycemic control; thus, as patients get closer to target A1C levels, PPG control is increasingly important. Adapted from Monnier L et al.<sup>33</sup>

hypoglycemia with the new insulin regimen. His A1C level remains essentially unchanged at 8.3%.

**Comment**

At this point, it is useful to look at the patient's daily blood glucose diary as recorded by SMBG at different time points (Table 7). His blood glucose at breakfast is not effectively controlled, which means more insulin is required at that time. His blood glucose is well controlled at midday and at the evening meal, but rises again before bedtime. He needs more insulin then, but during the night is experiencing hypoglycemia.

One approach to correcting this would be to increase the dose of his premixed insulin at the evening meal, but that may contribute to nocturnal hypoglycemia because the long-acting component of the premixed insulin will be present during the night (Figure 7, page 9). A better approach would be a regimen that combines basal insulin with a rapid-acting prandial insulin at the evening meal. This



**Figure 10. Comparison of daily glucose profiles after treatment with insulin glargine and twice-daily premixed insulin aspart.** After treatment with glargine, PPG excursions are evident, especially after the evening meal. Raskin P et al.<sup>34</sup>

would keep the PPG under control, but not lower glucose during the night.

**Second 3-Month Follow-Up Visit**

The patient is switched from premixed insulin to a basal-bolus regimen of glargine plus prandial insulin. The glargine dose is titrated to achieve an FPG of 100 to 110 mg/dL, starting with a dose that is about 60% of his total dose of premixed insulin. At 3 months,

**Table 7. Case Study Diary**

Daily Blood Glucose Diary									Week Ending _____
	Breakfast		Lunch		Dinner		MS		Middle of Night
	Dose	Blood Sugar	Dose	Blood Sugar	Dose	Blood Sugar	Dose	Blood Sugar	
Monday		147		110		153		185	57
Tuesday		138		112		170		164	48
Wednesday		140		90		155		205	–
Thursday		166		105		134		213	60
Friday									
Saturday									
Sunday									

**CASE STUDY** *(continued)*

FPG is well controlled with 75 U/d glargine, and A1C is 7.3%. With basal insulin, morning and overnight glycemic control is good, but glucose levels tend to rise in the evening, particularly after the evening meal (Figure 10). The clinician would like to lower the A1C further. The decision is made to add a rapid-acting insulin analog before the evening meal. Prandial therapy with glulisine is started at 5 U/d and titrated by using a treat-to-target algorithm.

**Comment**

For patients needing an additional insulin boost at the evening meal, the choices are regular insulin or rapid-acting insulin analogs. Currently available rapid-acting insulin analogs are aspart, lispro, and glulisine. A concern with adding regular insulin is its delayed onset of action and extended duration of action when it is no longer needed.<sup>35</sup> The advantage of rapid-acting prandial insulin is that it reaches peak effectiveness more quickly than regular insulin and is rapidly inactivated.<sup>35</sup>

Rapid-acting insulin provides a quick boost of insulin when needed after a meal and is eliminated rapidly, which limits the potential for hypoglycemia. Rapid-acting insulin analogs provide a more physiologic pattern of insulin than regular human insulin. The onset of action is 5 to 15 minutes, about half the time of regular insulin (30-60 minutes).<sup>36</sup> Peak action occurs 30 to 60 minutes after administration, and the duration of action is 4 to 6 hours. With regular insulin, peak action occurs 2 to 3 hours after administration, with a duration of action of up to 10 hours.<sup>36</sup>

**Clinical Decision Point**

*What is the best time to administer a rapid-acting insulin analog?*

- ➔ Before a meal
- ➔ After a meal
- ➔ Either works well

**Comment**

Regular human insulin should be administered 30 minutes prior to a meal, which is inconvenient for people with irregular mealtimes. If insulin is administered and the meal is delayed, the risk of hypoglycemia increases. However, regular human insulin is the standard of care against which new treatments must be measured. Rapid-acting analogs administered closer to the mealtime have an advantage only if they can achieve the same glycemic control as regular human insulin.

A study compared pre- and postmeal administration of insulin glargine with premeal administration of regular human insulin and found very similar levels of glycemic control. Patients in this study had type 1 diabetes; they received a basal-bolus regimen with glargine plus either glulisine (administered 0-15 minutes before or up to 20 minutes after the start of the meal) or regular human insulin administered 30 to 45 minutes prior to the meal.<sup>37</sup> Patients who received glulisine before or after meals had a lower incidence of severe hypoglycemia (8.4% each) than those who received regular human insulin (10.1%).<sup>37</sup>

**Case Study Summary**

Six months after starting the basal-bolus regimen, the patient's insulin dose is 70 U/d glargine plus 10 to 17 U glulisine after the evening meal. The glulisine dose is adjusted according to his carbohydrate consumption and amount of exercise that day by adding 1 U glulisine for every 25 mg/dL above 130 mg/dL measured on his SMBG after the meal. The basal/bolus regimen has reduced the episodes of hypoglycemia he experienced on the pre-mixed insulin regimen. His A1C level has remained <7%, and he feels well.

## QUESTIONS FROM SYMPOSIUM PARTICIPANTS

➔ **Q:** Can OADs ever be discontinued?

**A:** When patients do not achieve adequate control on appropriate OAD regimens, current recommendations are to continue all OADs and add/titrate basal insulin to achieve goals. At that point an attempt can be made to wean the OADs as follows:

1. Reduce the secretagogue to a low dose. The dose-response curve for sulfonylureas clearly shows minimal improvement with doses greater than half those recommended as maximal. In UKPDS, a low dose of ongoing secretagogue was shown to be more effective than insulin alone in patients with type 2 diabetes who still retain modest beta-cell reserves of endogenous insulin.
2. It is essential to know if the patient is being treated with a thiazolidinedione (TZD) and, if so, when it was added and what the impact was. Recent studies reinforce earlier hints that TZDs are most effective when used early in the course of type 2 diabetes.<sup>38,39</sup> If the patient had a prolonged period of good control, the treatment would most probably continue unchanged. On the contrary, if the TZD was added late (ie, as the third OAD) and failed to significantly lower the A1C, it should be dropped from the regimen.
3. Finally, continuing metformin in at least half-maximal doses should be considered to help overall glycemic control and as a hedge against weight gain.

When insulin is added to a therapeutic regimen for type 2 diabetes, it becomes the major player and a totally flexible tool for glycemic control. With careful glucose self-monitoring, OAD doses can be gradually weaned with safety and efficacy.

➔ **Q:** When can insulin be discontinued?

**A:** Patients with classic type 2 diabetes (middle-aged, overweight, not ketotic) may present with “glucose toxicity.” These individuals have very high glucose levels ( $\geq 300$ -500 mg/dL) and major symptoms of polyuria, polydipsia, and weight loss. They require prompt and aggressive insulin therapy for control (OADs are almost invariably ineffective) and symptomatic relief. Once glucose levels are under control, OADs can be considered and added as insulin doses gradually are tapered under conditions of careful glucose monitoring.

➔ **Q:** How do patients who don't have regular mealtimes control their glucose?

**A:** Basal insulin therapy is designed to provide a stable level of background insulin. The goal of basal insulin therapy is to keep the right balance of glucose when nothing unusual is added or removed. Even if a patient is eating intermittently, basal insulin therapy can be effective with little risk of hypoglycemia because patients with type 2 diabetes do have some residual insulin. If a meal is skipped, intrinsic insulin production usually can compensate. However, it is important to reinforce the benefit of regular mealtimes.

➔ **Q:** Is the initial dose of basal insulin titrated according to the patient's weight?

**A:** No. A patient's weight is taken into account only when it is outside the average: for example, an elderly woman with a low body weight. For such patients, the initial dose of insulin is approximately 10% of body weight in kilograms. For most patients, 10 U/d is a good starting dose that is low enough to avoid hypoglycemia.<sup>11</sup>

➔ **Q:** How is the dose of premixed insulin calculated?

**A:** It is difficult to determine the starting dose for an insulin that has 2 different components, which is part of the reason premixed insulin is not recommended during insulin titration. When a stable dose has been achieved, a good general guideline is that roughly 40% should be prandial insulin and 60% basal insulin. The dose can be back-calculated from there. For example, for a patient using a 70/30 premixed insulin aspart, the goal is to have the long-acting component roughly equal the current basal insulin and then calculate the prandial dose.

➔ **Q:** What is the role of inhaled insulin?

**A:** Inhaled insulin therapy is designed for thrice-daily administration, so it is more of a bolus-type than basal-type treatment strategy. Inhaled insulin has an extended duration of action that carries over to the next meal. Its uptake in the body is similar to rapid-acting insulins, and then slowly trails off. Patients treated with inhaled insulin have to be watched carefully for respiratory effects.<sup>40</sup> Inhaled insulin is contraindicated in smokers (they need to be abstinent for at least 6 months) and patients with severe asthma or emphysema, as well as anyone with an unexplained abnormal chest x-ray. Prior to initiation of premeal inhaled insulin, pulmonary function studies must be done to show a forced expiratory volume in 1 second (FEV<sub>1</sub>) at least 70% of predicted. This study needs to be repeated at 6 months and annually thereafter. Early studies have shown an almost 2.0% reduction in A1C in patients with type 2 diabetes who did not achieve control with OADs, and equivalent control to traditional insulin regimens. Inhaled insulin is not approved in pregnancy or in pediatric patients, and must be used with long-acting basal insulin in patients with type 1 diabetes.

Patients treated with inhaled insulin have to be cross-trained to self-administer subcutaneous injections because these injections may be necessary if respiratory illnesses develop. Inhaled insulin is an alternative, but until more data are available, it should be considered for patients who will not accept injections or who would otherwise delay insulin therapy because of concerns about injections.<sup>41</sup>

➔ **Q:** Is there still a role for bedtime insulin and regular insulin?

**A:** This regimen is effective, but not as effective as currently available options that more closely mimic the actions of the healthy pancreas. NPH at bedtime and regular insulin was the best option available a decade or more ago. However, because these agents did not closely mimic human physiology, there was a greater possibility of hypoglycemia. Hypoglycemia is a real fear and concern for

patients. Once it happens, they don't want to repeat that experience and that tends to keep them from getting too aggressive with their insulin. Any episode of major hypoglycemia must be avoided. The basal-bolus regimens that are used today are similar in concept to old-fashioned bedtime/regular insulin, but come closer to mimicking normal human physiology.

➔ **Q:** Why does insulin make a person hungry and how can this be offset?

**A:** Insulin is a hormone that stimulates the appetite. The question is how to keep patients from having excessive hunger when treated with insulin. The answer is to choose the most physiologic insulin regimen possible. A basal insulin comes closest to mimicking normal human physiology; insulin is not present when it is not needed. A rapid-acting analog insulin given at mealtime is metabolized quickly and, again, is not present when not needed, making it unlikely that the patient will be excessively hungry. One of the issues with premixed insulin is that there are periods during the day when there is insulin available that is not needed in a physiologic state.

➔ **Q:** Has measurement of A1C supplanted the 2-hour oral glucose tolerance test (OGTT) to diagnose diabetes?

**A:** It is important to realize that the A1C standard is not universal and is not used to diagnose diabetes. The diagnostic definition of diabetes is any fasting sugar >126 mg/dL or any plasma glucose 2 hours after eating >200 mg/dL or symptoms of diabetes plus a random glucose level (without regard to last meal) of 200 mg/dL.<sup>4</sup> The standard test is to administer a challenge equivalent to 75 g of anhydrous glucose dissolved in water and to measure the glucose level 2 hours later for patients whose random glucose levels are equivocal (ie, close to current diagnostic standards). Despite A1C being “unapproved” for strict diagnostic purposes, many clinicians use A1C levels to direct concerns and stratify therapy and follow-up.

The preference of some clinicians is to consider quartile of A1C for equivocal glucose readings, as shown in Table 8, given an upper normal level of 6.0% in the assay.

A schematic of this type begs the question of precise diagnosis but appropriately directs therapeutic concerns and actions.

➔ **Q:** What is the role of microalbumin in the evaluation of the need for insulin?

**A:** Microalbumin is a measure that can show detriments in tissue perfusion and microvascular blood supply. An increased level of microalbumin is a warning sign that can predate overt retinopathy, neuropathy, or nephropathy by about 10 years. However, all therapeutic decisions, including insulin initiation, should be driven by the patient's A1C level.

➔ **Q:** What is the value of the C-peptide test?

**A:** C-peptide is a marker for endogenous insulin reserve. If C-peptide is present, the patient is making insulin. The C-peptide test is not an absolute predictor; decisions about initiating or intensifying insulin therapy should be based on the patient's A1C level.

➔ **Q:** Is exenatide a good choice for a patient who is overweight?

**A:** Exenatide is appropriate for use with other oral agents in patients with diabetes and may be associated with weight loss. However, use of the drug primarily for weight loss is not approved for patients who do not have diabetes.



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