

# Early and Aggressive Initiation of Insulin Therapy for Type 2 Diabetes: What Is the Evidence?

Kevin Niswender, MD, PhD

**T**ype 2 diabetes mellitus is a progressive disease in which  $\beta$ -cell function continually declines and eventually fails, ultimately requiring nearly all patients to be placed on insulin therapy. An increasing body of evidence suggests that early intensive glycemic control reduces long-term vascular outcomes and potentially may prolong  $\beta$ -cell lifespan and function. Herein, evidence in favor of early insulin therapy on disease progression and long-term outcomes will be reviewed and placed into clinical context.

The importance of good glycemic control to reduce the risk of vascular complications of hyperglycemia is well established.<sup>4-7</sup> However, type 2 diabetes is a progressive disease, and the need for increasing the intensity of treatment to maintain glycemic control is an indicator of that progression. Ultimately, most patients will require insulin therapy, although insulin is still all too often thought of as “last resort” or “end-stage” therapy. This and other misperceptions frequently limit the early initiation of insulin therapy, even among patients for whom oral agents are no longer adequate.<sup>8,9</sup>

A variety of insulin analogs are now available that lower the risk of hypoglycemia and result in less weight gain, thus providing the tools to overcome barriers commonly associated with insulin therapy. New insulin analogs more closely mimic the kinetic profile of endogenous insulin and allow for flexible dosing

in pen devices that are generally well received by patients. Clinical outcome data, together with the safety and convenience of insulin analogs and newer insulin-delivery devices, may make early initiation of insulin therapy more attractive.

The objective of this review is to present recent clinical evidence in favor of early and aggressive blood-glucose lowering in patients with type 2 diabetes, and, in this context, to discuss and highlight real-world clinical experiences for type 2 diabetes disease management.

## Early and Aggressive Intervention Reduces Long-Term Vascular Risk

Cardiovascular disease is the major cause of morbidity and mortality in patients with diabetes.<sup>2</sup> In experi-

mental models, prolonged exposure to hyperglycemia has been shown to result in glucotoxicity<sup>10</sup> and oxidative stress,<sup>11-13</sup> culminating in  $\beta$ -cell destruction<sup>14</sup> and microvascular and macrovascular complications.<sup>13,15,16</sup> Thus, glycemic control is the primary therapeutic goal in the management of type 2 diabetes.

Three laboratory measures are recommended to gauge the level of glycemic control attained by individual patients (Table 1).<sup>17,18</sup> A1C values reflect glycemic exposure during a period of ~ 3 months. The expected A1C value for people with normal glucose metabolism is 4.0–6.0%.<sup>19</sup> Recommended target values for individuals with diabetes are < 7%<sup>17</sup> or  $\leq$  6.5%.<sup>18</sup> Individualized targets based on patients' entire clinical situation are also important.<sup>17</sup> Fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) values provide snapshots of basal glucose metabolism (i.e., hepatic glucose production) and, most importantly, exposure to postprandial glucose excursions, which have recently been linked to overall vascular damage.<sup>20</sup>

Tight glycemic control is crucial for reducing the incidence of retinopathy, nephropathy, and neuropathy in patients with diabetes, and evidence suggests that early control prevents macrovascular events many years down the road (i.e., induces a “metabolic memory”).<sup>4-7</sup> Results from the U.K. Prospective Diabetes Study (UKPDS) showed

### IN BRIEF

Type 2 diabetes is a progressive disease in which  $\beta$ -cell function continually declines and eventually fails, ultimately requiring nearly all patients to be placed on insulin therapy. An increasing body of evidence suggests that early intensive glycemic control reduces long-term vascular outcomes and potentially may prolong  $\beta$ -cell lifespan and function. Herein, evidence in favor of early insulin therapy on disease progression and long-term outcomes will be reviewed and placed into clinical context.

the end of the study.<sup>5</sup> In the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, a similar large effect of early glycemic control on cardiovascular events was noted.<sup>7</sup> Both the UKPDS and the DCCT/EDIC studies provide a strong rationale that early aggressive intervention in diabetes will dramatically lessen the burden of cardiovascular disease many years later.<sup>4–7</sup>

### Rationale for Early Initiation of Insulin Therapy

The fundamental scientific and clinical question of whether the progressive nature of diabetes can be modified remains of great interest. In proof of principle, the Diabetes Prevention Program demonstrated that an intensive lifestyle intervention was most effective at reducing progression to diabetes in high-risk individuals, followed by metformin therapy.<sup>22</sup>

There has been similar interest in understanding whether early intervention with insulin may be fundamentally disease-altering, potentially by protecting  $\beta$ -cell function.<sup>23–25</sup> A recent, randomized, parallel-group study of 382 patients with newly diagnosed type 2 diabetes provides intriguing support to this hypothesis.<sup>23</sup> The effects of intensive, short-term insulin therapy on  $\beta$ -cell function was evaluated in this trial, in which patients were randomly assigned to treatment with continuous subcutaneous insulin therapy, multiple daily insulin injections, or oral hypoglycemic agents.<sup>23</sup> Once patients achieved and sustained on-therapy normoglycemia for 2 weeks, pharmacological treatment was stopped.

Normoglycemia was attained by > 95% of patients in the insulin treatment groups compared to 84% of those receiving oral agents. Glycemic control was reached sig-

**Table 1. Goals for Glycemic Control**<sup>17,18</sup>

	ADA	AACE
A1C (%)	< 7	≤ 6.5
FPG (mg/dl)	70–130	< 110
PPG (mg/dl)	< 180	< 140

*ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.*

that aggressive glycemic control, with sulfonylureas or insulin in patients newly diagnosed with type 2 diabetes significantly reduced the risk of any microvascular endpoint compared to conventional treatment (relative risk [RR] reduction 25%;  $P = 0.0099$ ).<sup>4</sup> There was no significant difference in macrovascular risk among those treated intensively with chlorpropamide, glibenclamide, or insulin during the 10-year study period. Reduction in risk of myocardial infarction was of borderline significance with intensive glycemic control ( $P = 0.052$ ). No significant benefit was seen for other macrovascular endpoints.<sup>4</sup>

The results of a 10-year poststudy follow-up revealed the long-term benefit of early glycemic control in the UKPDS population.<sup>21</sup> At study end, the median A1C value was 7% in the intensive treatment group and 7.9% in the conventional treatment group, although values increased steadily during the 10-year study period.<sup>21</sup> After study end, the course of therapy was left to the discretion of the patients and their physicians, and differences in glycemic control had disappeared between treatment groups at the end of the first poststudy year. Glycemic control was similar during this follow-up period, and the A1C values were statistically similar across treatment groups during the course of the poststudy follow-up.<sup>21</sup>

Intriguingly, those who had received intensive treatment soon after diagnosis had significantly

lower rates of microvascular disease (RR = 0.76; 95% CI 0.64–0.89;  $P = 0.001$ ). In addition, these patients had lower rates of any diabetes-related endpoint (RR = 0.91; 95% CI 0.83–0.99;  $P = 0.04$ ), diabetes-related death (RR = 0.83; 95% CI 0.73–0.96;  $P = 0.01$ ), and death from any cause (RR = 0.87; 95% CI 0.79–0.96;  $P = 0.007$ ). A statistically significant reduction of risk for myocardial infarction was observed in patients who had been in the intensive treatment groups early (RR = 0.85; 95% CI 0.74–0.97;  $P = 0.01$ ) but who had similar glycemic control in the follow-up period.<sup>21</sup>

Results were further analyzed for the subgroup of overweight subjects at study entry and those who were treated with metformin rather than a sulfonylurea. During the poststudy follow-up, patients in the metformin group also initially showed lower risk of any diabetes endpoint (RR = 0.79; 95% CI 0.66–0.95;  $P = 0.01$ ), diabetes-related death (RR = 0.70; 95% CI 0.53–0.92;  $P = 0.01$ ), death from any cause (RR = 0.73; 95% CI 0.59–0.89;  $P = 0.002$ ), and myocardial infarction (RR = 0.67; 95% CI 0.51–0.89;  $P = 0.005$ ).<sup>21</sup>

Similar findings have been observed in the landmark Diabetes Control and Complications Trial (DCCT), in which intensive control prevented microvascular complications, despite the fact that glycemic control of the intensive group rapidly decayed to that of the “standard” therapy group at

nificantly faster with insulin, and at 1 year after treatment, 51% of those who had received continuous insulin and 45% of those who had received multiple daily insulin injections remained normoglycemic compared with 27% of patients randomized

to the oral treatment group.  $\beta$ -Cell function was measured at the end of therapy and after 1 year using homeostasis model assessment of basal  $\beta$ -cell function (HOMA B) and acute insulin response. Patients treated with continuous insulin

therapy had an increase in HOMA B of 160% compared to 105% for those treated with oral agents, an impressive, if not somewhat surprising, finding.<sup>23</sup> Another smaller study ( $n = 20$ ) found an immediate improvement in  $\beta$ -cell function after

**Table 2. Summary of OAD Interventions as Monotherapy<sup>27</sup>**

Intervention	Expected Decrease in A1C (%)	Advantages	Disadvantages
<b>Tier 1: Well-Validated Core</b>			
<b>Step 1: Initial therapy</b>			
Lifestyle changes to decrease weight and increase activity	1–2	Broad benefits	Insufficient for most in first year
Metformin	1–2	Weight neutral	Gastrointestinal side effects, contraindicated with renal insufficiency
<b>Step 2: Additional therapy</b>			
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	1–4 injections daily, monitoring, weight gain, hypoglycemia, high cost of analog insulin products
Sulfonylurea	1–2	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
<b>Tier 2: Less Well Validated</b>			
Thiazolidinedione	0.5–1.4	Improved lipid profile and potential decrease in myocardial infarction (with pioglitazone)	Fluid retention, congestive heart failure, weight gain, bone fractures, high cost, potential increase in myocardial infarction (with rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent gastrointestinal side effects, long-term safety not established, high cost
<b>Other Therapy</b>			
$\alpha$ -Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent gastrointestinal side effects, thrice-daily dosing, high cost
Glinide	0.5–1.5*	Rapidly effective	Weight gain, thrice-daily dosing, hypoglycemia, high cost
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent gastrointestinal side effects, long-term safety not established, high cost
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, high cost

\*Repaglinide is more effective in lowering A1C than nateglinide. Copyright 2009 American Diabetes Association. Reprinted with permission from Diabetes Care 32:93–203, 2009.

switching patients from sulfonylurea to preprandial rapid-acting insulin analog therapy.<sup>26</sup>

Finally, a 4-year randomized study of 49 patients who had been diagnosed with type 2 diabetes within 2 years of study entry compared the effects of insulin and glibenclamide on  $\beta$ -cell function, metabolic control, and quality of life.<sup>25</sup> Because glibenclamide stimulates endogenous insulin secretion, the study was designed to assess whether such stimulation accelerates  $\beta$ -cell failure. During the first year of treatment, A1C values were similar in the two treatment groups. However, during the next 3 years, glycemic control deteriorated faster in the glibenclamide group, and at year 4, A1C values were significantly higher than in the insulin treatment group ( $P = 0.04$ ).<sup>25</sup> Fasting insulin levels after acute treatment withdrawal were significantly higher in the insulin group throughout the study ( $P = 0.006$ ), suggesting that patients receiving insulin retained greater capacity for  $\beta$ -cell response and supporting the hypothesis that stimulation of endogenous insulin production may contribute to  $\beta$ -cell failure.<sup>25</sup> Of note, both treatments were well tolerated, and no significant effects on quality of life were measured between the two groups.<sup>25</sup>

Taken together, the results of these studies are consistent and suggest that early insulin supplementation may alter the progressive course of diabetes. This may be due to protection of, and possibly restoration of,  $\beta$ -cell function. More studies will clearly be required to verify and extend these findings and to understand specific biological mechanisms involved.

### Initiating Insulin Therapy

A range of pharmacotherapies other than insulin are available to meet the glucose-lowering needs of patients

across the spectrum of type 2 diabetes progression (Table 2).<sup>27</sup> Oral antidiabetic drugs (OADs) are often used as initial therapy.<sup>27</sup> Because type 2 diabetes is a progressive disease,  $\beta$ -cell mass and function gradually decrease to the point at which A1C levels rise despite the use of more than one OAD.<sup>28</sup>

During this progression, loss of glucose control with oral agents results in glucose toxicity and worsening pathophysiology. In experimental models, prolonged exposure to hyperglycemia has been shown to result in glucotoxicity and oxidative stress, culminating in  $\beta$ -cell destruction<sup>14</sup> and microvascular and macrovascular complications.<sup>15</sup> The timely addition of insulin to oral agents can prevent this cycle of disease progression and eliminate the “stuttering” pattern of loss of glycemic control.<sup>29</sup> Although treatment choices can and should be individualized to meet patient needs, the importance of achieving glycemic control should provide the clinical driving force in determining the treatment.

Insulin is clearly the most effective way to control blood glucose, but it also presents many therapeutic barriers for physicians and patients alike. As shown in Table 3, insulins with different pharmacodynamic profiles are available,<sup>18,30</sup> allowing for three possible strategies to initiate insulin therapy: 1) basal insulin, 2) basal/bolus insulin, or 3) premixed insulin.

Typically, the first strategy to consider is the early addition of a basal insulin to an OAD regimen. The long-acting basal insulin analogs insulin detemir and insulin glargine have a highly favorable pharmacodynamic profile (a long, relatively flat insulin time-action curve lasting up to 24 hours) that attenuates the risk of hypoglycemia.<sup>31</sup> Compared to neutral protamine Hagedorn (NPH) insu-

lin, both detemir and glargine have demonstrated comparable efficacy for glycemic control, a potential for once-daily dosing, and less hypoglycemia, and, with insulin detemir, a propensity toward less weight gain. Despite having fundamentally different pharmacological properties at the insulin molecule level, clinical trial data have shown that insulin detemir and insulin glargine have similar glycemic efficacy,<sup>32,33</sup> but somewhat different effects with respect to weight gain.<sup>32</sup>

Insulin detemir has consistently shown effective glycemic control accompanied by either weight loss or lower rates of weight gain compared to human insulins. In a 26-week, randomized, parallel-group trial, addition of twice-daily insulin detemir to oral therapy achieved a decrease in A1C of 1.8% compared to a decrease of 1.9% with NPH, and at study end, patients in the insulin detemir group had gained 1.6 kg less weight.<sup>34</sup> Detemir treatment also was associated with a 47% lower risk of hypoglycemia compared to NPH.<sup>34</sup>

Similar results were observed in a 22-week and a 26-week study.<sup>35,36</sup> Analysis of pooled data from > 900 patients with type 2 diabetes involved in a 22-week and a 24-week trial found that, although both treatments resulted in similar decreases in A1C values, patients receiving insulin detemir experienced minimal weight gain (< 1 kg), and those with the highest BMI actually lost weight. Patients with a BMI > 35 kg/m<sup>2</sup> had a mean loss of ~ 0.5 kg despite improvement in glycemic control.<sup>37</sup> In the NPH group, greater weight gain occurred regardless of baseline BMI, and with those with a BMI > 35 kg/m<sup>2</sup> gaining an average of ~ 2.4 kg.<sup>37</sup>

Treatment for 52 weeks with insulin glargine added to oral therapy also showed reduction in A1C levels similar to that achieved with NPH

**Table 3. Onset, peak, and duration of insulin actions<sup>18,30</sup>**

Insulin*	Onset	Peak	Effective Duration
Rapid-acting • Insulin aspart • Insulin lispro • Insulin glulisine	5–15 minutes	30–90 minutes	< 5 hours
Short-acting • Regular insulin	30–60 minutes	2–3 hours	5–8 hours
Intermediate (basal) • NPH	2–4 hours	4–10 hours	10–16 hours
Long-acting (basal) • Insulin glargine • Insulin detemir	Not applicable	Relatively flat	Up to 24 hours
Premixed • 75% lispro protamine/25% lispro • 70% aspart protamine/30% aspart • 70% NPH/30% regular	5–15 minutes 5–15 minutes 30–60 minutes	Dual Dual Dual	10–16 hours 10–16 hours 10–16 hours

\*Assumes 0.1–0.2 units/kg/injection. Onset and duration may vary by injection site.

(–0.8% vs. –0.7% with NPH), with lower rates of symptomatic hypoglycemia (33% vs. 51%;  $P = 0.027$ ).<sup>38</sup> However, weight gain was similar in the two treatment groups (+2.57 kg with insulin glargine vs. +2.34 kg with NPH).<sup>38</sup>

The weight findings associated with basal insulin analog use were confirmed in the open-label, prospective, observational PREDICTIVE study that enrolled 293 patients with type 2 diabetes who were switched to insulin detemir after treatment with NPH insulin or glargine in addition to oral agents.<sup>39</sup> Oral regimens remained the same, and the number of daily injections did not change. Regardless of their prior basal insulin regimen, patients achieved better glycemic control with insulin detemir; A1C decreased by 0.2% ( $P < 0.05$ ) among patients previously receiving NPH and by 0.6% ( $P < 0.0001$ ) for those who had originally received glargine. This improvement was accompanied by a weight decrease of 0.7 kg ( $P < 0.01$ ) in those previously prescribed NPH

and 0.5 kg ( $P < .5$ ) in patients who were switched from glargine.<sup>39</sup>

Weight gain of 2–4 kg is common after starting insulin therapy and is correlated with the extent of correction of hyperglycemia.<sup>27</sup> The incidence of total hypoglycemia also was reduced significantly in both groups ( $P < 0.0001$  for both comparisons), and these data provide important proof of principle that glycemic control can be improved with modern insulin analog therapy without excessive weight gain and hypoglycemia.<sup>39</sup>

Most patients will ultimately require prandial insulin in addition to basal insulin as  $\beta$ -cell function declines. Because diabetes is a heterogeneous disorder, some patients may require intensive basal/bolus therapy earlier than others. Basal/bolus therapy using rapid-acting insulin at mealtimes in addition to a basal insulin analog is highly effective and allows flexibility in both the timing and amount of prandial insulin dosing (Table 3).<sup>18,30</sup> Indeed, this type of regimen is considered

state-of-the-art and is clearly ideal for many patients with diabetes.

Premixed insulins may provide an easier means for achieving near-normal insulin profiles, but they provide less flexibility. Premixed biphasic insulins provide both a basal and prandial insulin component in a single injection and can be administered once or twice daily as initial therapy for type 2 diabetes. In some patients whose hyperglycemia is not adequately managed with oral agents, starting with biphasic insulin to provide basal and prandial insulin can be as effective as basal insulin plus metformin.<sup>40</sup> For example, the INITIATE study found that twice-daily biphasic insulin aspart 70/30 was more effective than glargine once daily in achieving target A1C levels, but it was associated with greater weight gain and more frequent minor hypoglycemic episodes.<sup>41</sup>

The 1-2-3 Study evaluated the efficacy and safety of biphasic insulin aspart 70/30 administered once-, twice-, or three times daily in patients with type 2 diabetes.<sup>42</sup> In

this 48-week observational study, 41% of patients achieved target A1C values of < 7% with once-daily dosing, 70% with twice-daily dosing, and 77% with thrice-daily dosing. Although the patients in this study were not necessarily recently diagnosed (patients were not included if they had been diagnosed < 12 months before study entry), the results showed that glycemic control can be achieved with biphasic insulin in patients for whom oral agents are not enough.<sup>42</sup>

Premixed combinations of rapid-acting insulin lispro plus long-acting protaminated lispro have been compared with basal insulin alone in randomized, open-label studies. In one such study, patients with type 2 diabetes, some of whom had received basal insulin injections previously, were randomized to receive insulin lispro 50/50 thrice daily plus metformin or insulin glargine once daily at bedtime plus metformin for 24 weeks.<sup>43</sup> At study end, those receiving premixed insulin lispro achieved better glycemic control (A1C = 7.1% with premixed insulin vs. 7.7% with once-daily basal insulin;  $P < 0.001$ ). The incidence of hypoglycemic episodes was statistically similar in the two groups (0.8 events per patient per 30 days with premixed lispro vs. 0.5 events per patient per 30 days with basal insulin glargine).<sup>43</sup>

In contrast, results from the PREFER study showed that basal/bolus insulin therapy (insulin detemir plus insulin aspart) and premixed biphasic insulin aspart 70/30 were equally effective in lowering A1C values for insulin-naive patients (mean decrease during 26 weeks, 1.69% with basal/bolus and 1.42% with biphasic insulin aspart 30%;  $P = 0.106$ ).<sup>44</sup> However, basal/bolus therapy was superior for patients with prior insulin use (mean decrease 1.21% with basal/bolus and 0.75% with biphasic insulin aspart

30%;  $P = 0.0129$ ). Rates of minor hypoglycemia were similar in both treatment groups. Major hypoglycemic episodes occurred in five patients in the basal/bolus group compared to none in the biphasic insulin group.<sup>44</sup> The reasons for the different results between the two studies are not clear, but they may be related to differences in patient populations or the different insulin formulations used.

Although the use of insulin analogs lowers the risks of hypoglycemia and weight gain compared to human insulin, these adverse effects still occur for some patients. In the study comparing lispro mix 50/50 with basal insulin glargine, minor hypoglycemic episodes occurred in 46% of those receiving the premix and 52% of those receiving basal insulin glargine combined with prandial insulin lispro.<sup>43</sup> Nonetheless, intensive patient education regarding initiating insulin therapy, treating hypoglycemia, monitoring blood glucose, and improving diet and lifestyle can alleviate concerns and increase the likelihood of safe and successful treatment.<sup>45</sup>

### Implications for Clinical Practice

The following case studies are designed to illustrate real-world clinical situations in which initiation of insulin therapy may represent a good therapeutic choice.

**Case 1.** John was a 63-year-old African-American office worker with a BMI of 37 kg/m<sup>2</sup>. His diet was high in carbohydrates, fat, and salt, and he got little exercise. His A1C was 11.2%, and his FPG was 280 mg/dl. His initial therapy consisted of metformin 2,000 mg daily, plus a diet and exercise plan. At his 3-month follow-up visit, his A1C was 9.4%, and his FPG was 210 mg/dl. Thus, in this first case, glycemic control was not achieved after 3 months of therapy with metformin and lifestyle

changes in a patient newly diagnosed with type 2 diabetes.

The initial therapy prescribed for John was the maximum dose of metformin in combination with lifestyle interventions. Metformin is a good choice for an oral agent because it is weight-neutral and inexpensive and can lower A1C values by 1.5% (Table 2).<sup>27</sup> Weight loss and dietary changes are crucial to achieving glycemic control and ideally will result in A1C decreases of 1 or 2%. After 3 months, however, John's A1C, although lower, was still well above the target value.

One approach to increasing the intensity of his therapy would be to add a second oral agent to the existing regimen in the form of a sulfonylurea. However, a recent meta-analysis has shown that adding a sulfonylurea to metformin is unlikely to reduce A1C by > 1%,<sup>46</sup> and deterioration of glycemic control after addition of a sulfonylurea to metformin is frequent within 6 months.<sup>47</sup> Moreover, this approach is associated with weight gain and a higher incidence of hypoglycemic events.<sup>46</sup>

Initiating a basal insulin regimen in addition to the second OAD may allow the patient to control his hyperglycemia but will not reduce the effect on his weight. The American Association of Clinical Endocrinologists (AACE) recommends that treatment-naive individuals whose initial A1C value is > 10% be started on insulin therapy.<sup>18</sup> Consistent with these recommendations, John could be started on a long-acting insulin, such as insulin detemir or insulin glargine. Initiation of long-acting insulin might be expected to reduce the A1C level by 2–2.5%, avoiding the addition of a second oral agent.<sup>27</sup>

Other alternatives might include an oral dipeptidyl peptidase-4 (DPP-4) inhibitor (i.e., sitagliptin

tin) or a long-acting glucagon-like peptide 1 (GLP-1) analog, although neither would be predicted to be as efficacious in this patient, whose A1C-lowering goal is still nearly 2.5%.

**Case 2.** Bob was a 58-year-old man with hypertension, dyslipidemia, and type 2 diabetes. His BMI was 32 kg/m<sup>2</sup>, and his weight was 83 kg. His A1C was 8.5%, his FPG was 160 mg/dl, and his PPG was 218 mg/dl. He was being managed with metformin 1,000 mg twice daily plus pioglitazone, 30 mg daily, and glimepiride, 4 mg daily. In this case, the common experience of weight gain after switching from OAD therapy to NPH insulin therapy is discussed.

Bob's case illustrates a common therapeutic consideration. He was overweight, had the dyslipidemia characteristic of diabetes, obesity, and metabolic syndrome (triglycerides of 300 mg/dl; HDL cholesterol of 28 mg/dl), and elevated fasting and postprandial glucose readings. At his first office visit, Bob had an A1C level of 8.5%, an FPG of 160 mg/dl, a PPG of 218 mg/dl, and a cholesterol level of 190 mg/dl. His doctor started him on 10 units of NPH insulin at bedtime, and that dose was gradually increased during the next 6 months.

At his 6-month follow-up visit, Bob's A1C value had decreased to 7.3%. However, he had gained 6.7 kg and had a worsening lipid profile. Despite his glycemic control, the patient was frustrated that he was gaining despite eating a healthier diet and exercising regularly.

Bob may be a good candidate to switch from NPH insulin to either insulin glargine or insulin detemir. Some of his weight gain may be due to either clinically significant or undetected hypoglycemia or anticipation of hypoglycemia; hypoglycemia is a potent stimulus to feed. Although both glargine and detemir

may offer significant improvement in this regard, some distinctions are worth noting. As noted above, detemir has been shown in several randomized clinical trials to cause significantly less weight gain.<sup>32,34,35,37,39,48,49</sup>

The mechanism by which weight gain is attenuated with insulin detemir is not fully understood. A 26-week, open-label study suggested that the weight-sparing effects of insulin detemir are independent of rates of hypoglycemia.<sup>50</sup> Efforts are ongoing to identify the biochemical and physiological mechanisms that account for the lower weight gain experienced with insulin detemir.

**Case 3.** Nicole was a 17-year-old African-American student with a BMI of 25 kg/m<sup>2</sup>. Upon presentation, her A1C was 8.6%, and her FPG was 231 mg/dl. She had a positive family history of type 2 diabetes and had experienced weight loss and symptoms of polyuria and polydipsia. Thus, in this case, a patient with new-onset diabetes (presumed to be type 2 diabetes) was started on metformin, 500 mg twice daily, and a split-mixed insulin regimen of NPH and lispro, in addition to fluids and given diabetes education.

At her 1-month follow-up visit, she was found to be positive for islet cell autoantibodies, GAD antibodies, and ICA-512 antibodies, all of which are diagnostic of type 1 rather than type 2 diabetes. Her A1C was 7.8%. Her metformin was discontinued because of her positive antibody studies, but her insulin regimen was continued. At her 3-month follow-up, Nicole's A1C was 5.9%.

With her African-American race and family history of diabetes, combined with the growing prevalence of type 2 diabetes, many physicians would have assumed that she had type 2 diabetes. Fortunately, her physician screened for antibodies against  $\beta$ -cells, clearly identifying

her disease as autoimmune-mediated type 1 diabetes. She also had evidence of insulin resistance that may be referred to as "double diabetes." Had the correct diagnosis not been made and had she continued treatment with metformin monotherapy, the disease may have progressed to diabetic ketoacidosis. The use of other secretagogues would also have been counterproductive and contraindicated. Finally, the insulin regimen chosen reflects thoughtful attention to treating both fasting and postprandial hyperglycemia.

### Conclusions

These clinical case studies exemplify the diversity of patients who may benefit from early insulin initiation. Ultimately, it is hoped that early initiation of therapy will not only prevent short-term complications, but also reduce long-term morbidity and mortality and potentially alter the natural history of the disease. This latter concept is currently of intense interest.

Although optimal disease management is patient-specific, achieving and maintaining tight glycemic control are the primary goals of therapy. Because many type 2 diabetic patients will eventually require insulin therapy, overcoming fears and therapeutic barriers to initiating therapy early as needed are essential for reducing the vascular comorbidities of this highly prevalent disease in patients of all ages. Fortunately, a number of new clinical tools are available, including both prandial and basal insulin analogs, new insulin-delivery devices, and an ever-improving knowledge of the pathophysiology and natural history of diabetes.

### ACKNOWLEDGMENTS

The author wishes to thank Ann C. Sherwood, PhD, of DesignWrite, LLC, for providing writing and edito-

rial assistance. Funding to support the preparation of this manuscript was provided by Novo Nordisk, Inc.

## REFERENCES

- <sup>1</sup>World Health Organization: What is diabetes? [article online] Available from <http://www.who.int/mediacentre/factsheets/fs312/en/>. Accessed 19 March 2009
- <sup>2</sup>National Institutes of Health: National diabetes statistics 2007—prevalence of diagnosed and undiagnosed diabetes in the United States, all ages, 2007 [article online]. Available from <http://diabetes.niddk.nih.gov/dm/pubs/statistics/#allages>. Accessed 19 March 2009
- <sup>3</sup>Lloyd-Jones D, Adams R, Carnethon M, De SG, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smolter S, Wong N, Wylie-Rosett J, Hong Y: Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 119:480–486, 2009
- <sup>4</sup>U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
- <sup>5</sup>DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
- <sup>6</sup>U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
- <sup>7</sup>Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
- <sup>8</sup>Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, Landgraf R, Kleinbreil L: Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 28:2673–2679, 2005
- <sup>9</sup>Nichols GA, Koo YH, Shah SN: Delay of insulin addition to oral combination therapy despite inadequate glycemic control: delay of insulin therapy. *J Gen Intern Med* 22:453–458, 2007
- <sup>10</sup>Prentki M, Nolan CJ: Islet beta cell failure in type 2 diabetes. *J Clin Invest* 116:1802–1812, 2006
- <sup>11</sup>Hartge MM, Unger T, Kintscher U: The endothelium and vascular inflammation in diabetes. *Diabetes Vasc Dis Res* 4:84–88, 2007
- <sup>12</sup>Ceriello A, Bortolotti N, Motz E, Pieri C, Marra M, Tonutti L, Lizzio S, Feletto F, Catone B, Taboga C: Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia. *Metabolism* 48:1503–1508, 1999
- <sup>13</sup>Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295:1681–1687, 2006
- <sup>14</sup>Steppell JH, Horton ES: Beta-cell failure in the pathogenesis of type 2 diabetes mellitus. *Curr Diab Rep* 4:169–175, 2004
- <sup>15</sup>Unger J, Cole BE: Recognition and management of diabetic neuropathy. *Prim Care* 34:887–913, 2007
- <sup>16</sup>Brownlee M: The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 54:1615–1625, 2005
- <sup>17</sup>American Diabetes Association: Standards of medical care in diabetes—2009. *Diabetes Care* 32 (Suppl. 1):S13–S61, 2009
- <sup>18</sup>Jellinger PS, Davidson JA, Blonde L, Einhorn D, Grunberger G, Handelsman Y, Hellman R, Lebovitz H, Levy P, Roberts VL: Road maps to achieve glycemic control in type 2 diabetes mellitus [article online]. Available from <http://www.aace.com/meetings/consensus/odimplementation/roadmap.pdf>. Accessed 19 March 2009
- <sup>19</sup>Cooper DH: *The Washington Manual of Medical Therapeutics*. 32nd ed. Cooper DH, Ed. Philadelphia, Pa., Lippincott Williams & Wilkins, 2007
- <sup>20</sup>Tibaldi J: Importance of postprandial glucose levels as a target for glycemic control in type 2 diabetes. *South Med J* 102:60–66, 2009
- <sup>21</sup>Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA: 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359:1577–1589, 2008
- <sup>22</sup>DPP Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
- <sup>23</sup>Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, Hu Y, Zhou Z, Yan X, Tian H, Ran X, Luo Z, Xian J, Yan L, Li F, Zeng L, Chen Y, Yang L, Yan S, Liu J, Li M, Fu Z, Cheng H: Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 371:1753–1760, 2008
- <sup>24</sup>Pfutzner A, Schondorf T, Seidel D, Winkler K, Matthaei S, Hamann A, Forst T: Impact of rosiglitazone on beta-cell function, insulin resistance, and adiponectin concentrations: results from a double-blind oral combination study with glimepiride. *Metabolism* 55:20–25, 2006
- <sup>25</sup>Alvarsson M, Sundkvist G, Lager I, Berntorp K, Fernqvist-Forbes E, Steen L, Orn T, Holberg MA, Kirksaether N, Grill V: Effects of insulin vs. glibenclamide in recently diagnosed patients with type 2 diabetes: a 4-year follow-up. *Diabetes Obes Metab* 10:421–429, 2008
- <sup>26</sup>Pfutzner A, Lorra B, Abdollahnia MR, Kann PH, Mathieu D, Pehner C, Oligschleger C, Kaiser M, Forst T: The switch from sulfonylurea to preprandial short-acting insulin analog substitution has an immediate and comprehensive  $\beta$ -cell protective effect in patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 8:375–384, 2006
- <sup>27</sup>Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B: Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 32:193–203, 2009
- <sup>28</sup>Riedel AA, Heien H, Wogen J, Plauschinat CA: Secondary failure of glycemic control for patients adding thiazolidinedione or sulfonylurea therapy to a metformin regimen. *Am J Manag Care* 13:457–463, 2007
- <sup>29</sup>Brunton S: Initiating insulin therapy in type 2 diabetes: benefits of insulin analogs and insulin pens. *Diabetes Technol Ther* 10:247–256, 2008
- <sup>30</sup>American Association of Clinical Endocrinologists Diabetes Mellitus Clinical Practice Guidelines Task Force: American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus [article online]. Available from <http://www.aace.com/pub/pdf/guidelines/DMGuidelines2007.pdf>. Accessed 19 March, 2009
- <sup>31</sup>Heise T, Pieber TR: Towards peakless, reproducible and long-acting insulins: an assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes Obes Metab* 9:648–659, 2007
- <sup>32</sup>Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthaner G: A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia* 51:408–416, 2008
- <sup>33</sup>King AB: Once-daily insulin detemir is comparable to once-daily insulin glargine in providing glycaemic control over 24 h in patients with type 2 diabetes: a double-blind, randomized, crossover study. *Diabetes Obes Metab* 11:69–71, 2009
- <sup>34</sup>Hermansen K, Davies M, Dereziński T, Ravn GM, Clauson P, Home P: A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering

drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 29:1269–1274, 2006

<sup>35</sup>Haak T, Tiengo A, Draeger E, Sunyum M, Waldhausl W: Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab* 7:56–64, 2005

<sup>36</sup>Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N: Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract* 66:193–201, 2004 [Correction appears in *Diabetes Res Clin Pract* 72:112, 2006]

<sup>37</sup>Raslova K, Tamer SC, Clauson P, Karl D: Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. *Clin Drug Invest* 27:279–285, 2007

<sup>38</sup>Yki-Jarvinen H, Dressler A, Ziemien M: Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 23:1130–1136, 2000

<sup>39</sup>Dornhorst A, Luddeke HJ, Koenen C, Merilainen M, King A, Robinson A, Sreenan S: Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE. *Diabetes Obes Metab* 10:75–81, 2008

<sup>40</sup>Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P: Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin

aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. *J Diabetes Complications* 17:307–313, 2003

<sup>41</sup>Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A: Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 28:260–265, 2005

<sup>42</sup>Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, Jain R: Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1-2-3 study). *Diabetes Obes Metab* 8:58–66, 2006

<sup>43</sup>Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, Milicevic Z, Jones CA, Sarwat S, Tan MH: Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA<sub>1c</sub> and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. *Clin Ther* 29:2349–2364, 2007

<sup>44</sup>Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B: Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab* 11:45–52, 2009

<sup>45</sup>Mulcahy K: Diabetes self-management education core outcomes measures. *Diabetes Educ* 29:768–803, 2003

<sup>46</sup>Belsey J, Krishnarajah G: Glycaemic control and adverse events in patients with type 2 diabetes treated with metformin + sul-

phonylurea: a meta-analysis. *Diabetes Obes Metab* 10 (Suppl. 1):1–7, 2008

<sup>47</sup>Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR: Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. *Diabetes Care* 28:995–1000, 2005

<sup>48</sup>Meneghini L, Koenen C, Weng W, Selam JL: The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes: results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab* 9:902–913, 2007

<sup>49</sup>Fajardo Montanana C, Hernandez Herrero C, Rivas Fernandez M: Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients: the PREDICTIVE BMI clinical trial. *Diabet Med* 25:916–923, 2008

<sup>50</sup>Davies MJ, Dereziński T, Pedersen CB, Clauson P: Reduced weight gain with insulin detemir compared to NPH insulin is not explained by a reduction in hypoglycemia. *Diabetes Technol Ther* 10:273–277, 2008

---

Kevin Niswender, MD, PhD, is a staff physician in the Department of Veterans Affairs Tennessee Valley Healthcare System and an assistant professor in the Department of Medicine, Division of Diabetes, Endocrinology, and Metabolism at Vanderbilt University School of Medicine, in Nashville, Tenn.