

Management of Type 2 Diabetes Mellitus with Basal-Prandial Insulin Therapy: A Case-Based Review

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ABSTRACT

Background: Diabetes mellitus (DM) is a growing epidemic in the United States—20.8 million people are affected and 90% to 95% of all diagnosed cases are type 2 DM. Nevertheless, implementation of insulin therapy is often delayed in patients with type 2 DM. This delay can increase the risk of DM-related complications, including microvascular neuropathy, nephropathy, retinopathy, and cardiovascular disease.

Objective: This article provides a case-based review outlining a novel strategy for advancing therapy with a modified basal and prandial insulin regimen to achieve recommended glycemic targets in type 2 DM as quickly as possible. Evidence-based treatment strategies are also discussed.

Methods: Materials used for this article were identified through an English-language literature search of MEDLINE (1967–2007) using the following terms: *insulin*, *postprandial glucose control*, and *type 2 diabetes*.

Results: As shown with this male 46-year-old case study patient, type 2 DM is treated initially with diet and exercise, followed by oral antidiabetic drugs (OADs). However, oral therapy typically reduces glycosylated hemoglobin values only by ~1.5% to 2.0%. Intensive therapy with once-daily basal insulin in combination with a previously prescribed OAD regimen can achieve normoglycemia and reduce the long-term complications of DM. In patients with postprandial glucose excursions, prandial insulin can be added using a rapid-acting insulin analogue (aspart, lispro, or glulisine).

Conclusions: A key factor in this case patient's ability to reach glycemic targets within 1 year of diagnosis of type 2 DM was the accelerated implementation of insulin therapy. Such a therapeutic approach obviates the risk for uncontrolled hyperglycemia, which is associated with the standard practice of beginning treatment with diet and exercise alone and slowly advancing by 1 OAD at a time, ending with insulin therapy as a last resort. (*Insulin*. 2007;2:118–126) Copyright © 2007 Excerpta Medica, Inc.

Key words: type 2 diabetes mellitus, hyperglycemia, insulin, complications.

INTRODUCTION

In the United States, diabetes mellitus (DM) is a growing epidemic, currently affecting 20.8 million people, or 7% of the population; 90% to 95% of all diagnosed cases are type 2 DM.¹ A number of factors contribute to this worsening epidemic, including continual increases in the prevalence of obesity and other lifestyle factors associated with DM, as well as changes in the demographic composition of the population.² Several racial groups (ie, blacks, Hispanics, Asians, Native Americans) are at particularly high risk for developing type 2 DM,³ and projections for the next 50 years estimate that the highest percent increases in the prevalence of DM will occur among minorities and the elderly (ie, those aged ≥75 years).² Currently, there is an increasing prevalence of type 2 DM among adolescents.⁴

DM is associated with the risk of developing several long-term morbidities, including microvascular and macrovascular complications. Development of type 2 DM at earlier ages, coupled with delayed diagnosis and/or inadequate treat-

ment, can lead to increased exposure to microvascular neurologic damage.⁵ Patients with type 2 DM are also at an increased risk of developing cardiovascular disease. In fact, the risk for myocardial infarction (MI) in patients with type 2 DM and no history of MI can equal that of nondiabetic patients who have experienced a heart attack.⁶

It has been found that intensive therapy to achieve normoglycemia can reduce the long-term complications associated with DM. For example, an analysis from the United Kingdom Prospective Diabetes Study reported that each 1.0% reduction in mean glycosylated hemoglobin (A1C) concentration was associated with a 21% reduction in risk for any DM-related end point ($P < 0.001$), a 37% reduction in microvascular complication risk ($P < 0.001$), and a 14% reduction in the risk for MI ($P < 0.001$).⁷ There was no threshold of risk (ie, any reduction in A1C can lessen the risk of complications), but the lowest risk was observed in patients whose A1C values were within the normal range (ie, <6.0%). The Steno-2 Trial⁸ assessed patients with type 2 DM treated

with an intensive, target-driven, multifactorial intervention that included behavioral modification and oral antidiabetic drugs (OADs), followed by insulin therapy when patients did not reach glycemic goals (ie, A1C <6.5%). In addition, these patients received pharmacologic therapy targeting hypertension, dyslipidemia, and microalbuminuria, and used acetylsalicylic acid (ASA) for secondary prevention of cardiovascular disease. Patients receiving this intensive therapy had a significantly lower risk ($P < 0.01$) of microvascular and macrovascular complications than patients who received conventional treatment, which included less aggressive target goals, fewer medications at lower dosages, and less ongoing DM education.

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Based on a substantial body of epidemiologic evidence concerning the benefits of good glycemic control, current American Diabetes Association (ADA) recommendations for patients with type 2 DM call for the primary target, the A1C concentration, to be <7.0% or as close to normal (ie, <6.0%) as possible without inducing hypoglycemia, as well as for fasting plasma glucose (FPG) levels of 90 to 130 mg/dL and postprandial glucose (PPG) levels of <180 mg/dL (Table I).⁹ The glycemic targets of the American Association of Clinical Endocrinologists are even lower.¹⁰

This article provides a case-based review outlining a novel strategy for advancing therapy with a modified basal and prandial insulin regimen to achieve recommended glycemic targets in type 2 DM as quickly as possible. Evidence-based treatment strategies are also discussed. The flowchart in the figure gives an overview of the stepwise procedure.

MATERIALS AND METHODS

Materials used for this article were identified through an English-language literature search of MEDLINE (1967–2007) using the following terms: *insulin, postprandial glucose control, and type 2 diabetes*.

CASE STUDY

Patient Description and Initial Diagnosis

E.L. is a 46-year-old man undergoing an annual physical examination. He has not been experiencing symptoms attributable to hyperglycemia, but he has reported a lower-than-normal energy level over the past year. The patient is a nonsmoker and, as a former Navy Seal, has been in good physical condition throughout his life. However, he has a history of chronic back pain (due to a parachute injury), which has started to limit his degree of physical activity. At the current visit, his height and weight were 6 ft 3 in and 260 lb, for a body mass index of 32.5 kg/m² (reaching the clas-

Table I. American Diabetes Association (ADA)-recommended targets for glycemic control, blood pressure, and lipid parameters in patients with type 2 diabetes mellitus.⁹

Parameter	ADA-Recommended Level
Glycemic control*	
A1C	<7.0% [†]
Preprandial plasma glucose	90–130 mg/dL
Peak postprandial glucose	<180 mg/dL [‡]
Blood pressure	<130/80 mm Hg
Lipids	
LDL-C	<100 mg/dL
Triglycerides	<150 mg/dL
HDL-C	>40 mg/dL

A1C = glycosylated hemoglobin; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

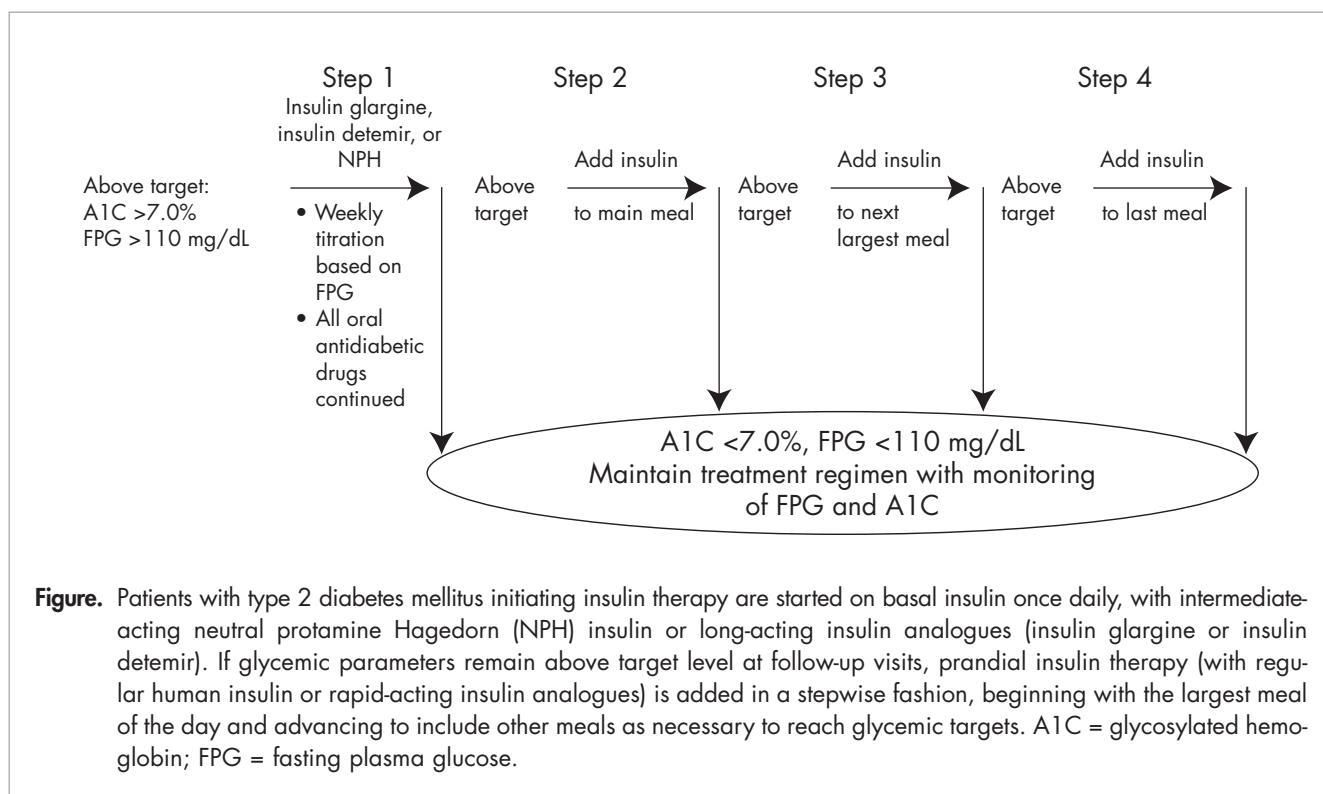
*Glycemic goals recommended by the American Association of Clinical Endocrinologists are even lower: A1C, ≤6.5%; fasting/preprandial plasma glucose, <110 mg/dL; and 2-hour postprandial plasma glucose, <140 mg/dL.¹⁰

[†]The A1C goal for the patient is an A1C as close to normal (ie, <6.0%) as possible without significant hypoglycemia. The A1C goal for patients in general is <7.0%.

[‡]One- to 2-hour peak postprandial capillary plasma glucose.

sification for obesity). He also has a family history of type 2 DM (mother) and hypothyroidism (grandmother), as well as a medical history of hypertension and dyslipidemia. The physical examination and laboratory results showed a blood pressure reading of 143/87 mm Hg, a low-density lipoprotein cholesterol (LDL-C) level of 128 mg/dL, a high-density lipoprotein cholesterol (HDL-C) level of 38 mg/dL, a triglyceride (TG) level of 210 mg/dL, and a C-peptide level of 0.5 nmol/L, indicating some endogenous insulin-secreting capacity. His microalbumin level was 53 µg/dL, indicating endothelial dysfunction and macrovascular risk. His liver function test results and creatinine level were within normal range. He had a thyroid-stimulating hormone (TSH) value of 16 mIU/mL, a free T₄ level of 0.8 ng/dL, a random blood glucose value of 263 mg/dL, and an A1C of 9.6%. The resulting diagnosis was type 2 DM and hypothyroidism.

The patient was educated regarding a healthy diet, an appropriate exercise plan, and self-monitoring of blood glucose (SMBG), and the following treatment regimen was prescribed: (1) 2 OADs (metformin 500 mg twice daily, to be increased over 4 weeks to 1000 mg twice daily, and glimepiride 2 mg once daily); (2) a statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) to reduce cholesterol levels (pravastatin 20 mg once daily); (3) an angiotensin-converting enzyme inhibitor to lower blood pressure and protect against nephropathy (lisinopril 20 mg



once daily); (4) levothyroxine 100 µg once daily; and (5) ASA 162 mg once daily. He was instructed to perform SMBG twice daily and was scheduled for a 3-month follow-up visit.

Treatment Strategies

Typically, the initial approach to treating type 2 DM is diet and exercise, followed by a stepwise introduction of OADs. Treatment often is initiated after the patient has been hyperglycemic for a significant period of time, and the stepwise approach traditionally has been implemented slowly, with long delays between steps.⁵ This strategy exposes the patient to extended periods of hyperglycemia and an accumulation of its associated morbidities, including nephropathy, retinopathy, neuropathy, and cardiovascular disease.¹ Often, by the time the patient receives insulin therapy as a last resort to achieve glycemic control, he or she has had DM for 10 to 15 years and already has established DM-related complications. Moreover, β-cell dysfunction—at least transiently—may improve when hyperglycemia is lowered early in the course of disease, but this opportunity could be missed with delays in treatment.^{5,11} For these reasons, the patient in this case—who had an A1C value of 9.6% at diagnosis—was immediately started on a treatment plan, includ-

ing diet, exercise, and combination therapy with 2 OADs (a sulfonylurea and metformin).

Medications targeting the patient's hypertension and dyslipidemia were initiated earlier in the treatment of this patient's DM as a way to limit the associated microvascular and macrovascular diseases.¹² It should be noted that the risk of rhabdomyolysis is elevated in patients with hypothyroidism, and creatine phosphokinase levels must be closely monitored.¹³ ASA was included in this patient's treatment regimen to prevent cardiovascular events. Although there is no evidence to support the prescribing of specific doses in patients with type 2 DM, a range of ASA 75 to 325 mg/d has been reported in most clinical trials.⁹ A mid-range dose of 162 mg of ASA was chosen, which would confer cardiovascular protection without undue risk of adverse effects. Levothyroxine was added to treat the patient's hypothyroidism, but it is important to monitor the dose of this agent in patients with type 2 DM, as it may affect the symptoms of DM.¹⁴

Importantly, sulfonylureas and metformin have complementary mechanisms of action that address the 2 core defects of type 2 DM: deficiency in endogenous insulin secretion and insulin resistance. Sulfonylureas stimulate insulin secretion, whereas metformin primarily decreases hepatic glucose output (and is an insulin sensitizer).¹⁵ Other classes of available OADs include the thiazolidinediones (TZDs), which also act as insulin sensitizers; nonsulfonylurea secretagogues (glitinides), which also stimulate insulin secretion; and α-glucosidase inhibitors, which delay carbohydrate absorption in the small intestine.¹⁶

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A new class of OADs, the dipeptidyl peptidase–IV inhibitors, has recently become available. These agents inhibit the inactivation of incretins, hormones that enhance glucose-dependent insulin secretion and regulation of glucagon release.¹⁷ Sitagliptin has been approved as monotherapy or in combination with metformin, pioglitazone, or rosiglitazone for the treatment of type 2 DM. Sitagliptin has been demonstrated to improve glycemic control by a mean A1C of 0.7%.¹⁸

Regardless of the OADs chosen (as monotherapy or in combination), oral therapy typically can be expected to reduce A1C values by only ~1.5% to 2.0%, and the improvement is slow, with extended periods of time between treatment modification steps.^{5,16} One recent study reported that the degree of A1C reduction within the first year of monotherapy with metformin was the best predictor for avoiding secondary failure of metformin therapy (defined as the switch to or the addition of an OAD).¹⁹ Results from this study also demonstrated that patients who did not reach an A1C level of <8.0% within the first year of metformin therapy had worse A1C levels at treatment initiation than those who did reach this A1C level within 1 year (9.7% vs 8.6%; $P < 0.001$).¹⁹ This supports the observation that patients with very high A1C values at baseline (such as the patient in the current case [9.6%]) are unlikely to achieve adequate glycemic control with OAD monotherapy (ADA-recommended A1C $\leq 7.0\%$ and American Association of Clinical Endocrinologists–recommended A1C $\leq 6.5\%$).^{9,10}

Patient Follow-Up after 3 Months of Treatment: Inadequate Glycemic Control

At his 3-month follow-up visit, E.L. showed considerable improvement in glycemic control, although his glycemic parameters remained substantially above ADA recommendations: his A1C was 7.8%, and 2-week SMBG results were consistently above 100 mg/dL, ranging from a morning FPG level of ~150 mg/dL to an evening PPG level of ~200 mg/dL. The patient reported exercising for 30 minutes 3 to 4 times per week. His weight, however, was relatively unchanged at 258 lb. His blood pressure and lipid parameters were all slightly improved (blood pressure, 138/84 mm Hg; LDL-C, 105 mg/dL; HDL-C, 41 mg/dL; TG, 191 mg/dL) but still above ADA recommendations. Free T₄ and TSH levels were normal (1.6 ng/dL and 3.6 mIU/mL, respectively).

Therefore, the patient's new treatment plan included an increase in the dosages of lisinopril (to 40 mg once daily) and pravastatin (to 30 mg once daily [the patient had not experienced any adverse effects from the initial dose of pravastatin]) and the addition of hydrochlorothiazide 25 mg. More aggressive hyperglycemic therapy was also initiated: metformin therapy was maintained at 1000 mg twice daily; levothyroxine was maintained at 100 µg once daily; ASA was maintained at 162 mg once daily; glimepiride was increased to 4 mg once daily; and basal insulin therapy using insulin glargine was initiated at 20 IU once daily. The insulin glargine dose would be increased weekly by 2 IU if the mean

blood glucose was <150 mg/dL and by 4 IU if the mean blood glucose was >150 mg/dL until FPG was <110 mg/dL. The patient also was scheduled for a follow-up visit in an additional 3 months to assess the modified treatment plan.

Treatment Strategies

Insulin is regarded as a highly effective therapy for achieving glycemic goals in patients with type 2 DM. In fact, data suggest that the early use of insulin in these patients may result in disease remission. In a study of 13 newly diagnosed patients whose type 2 DM was unresponsive to dietary intervention alone,²⁰ a 2-week course of treatment with continuous subcutaneous insulin infusion induced remission in 9. These patients were then maintained on diet alone and achieved adequate glycemic control for 9 to >50 months. However, insulin therapy is often delayed in patients with type 2 DM due to patient fears regarding injection or concerns about hypoglycemia. Because of these obstacles to treatment, it is crucial for the health care professional to educate patients about insulin therapy so that these individuals are encouraged and motivated to adhere to treatment regimens. If available, a DM educator can address “needle phobia” by assuring patients that current needles are considered almost painless and that easy-to-use injection systems are available.²¹ Fear of hypoglycemia can be allayed by instructing patients that hypoglycemic events occurred more often with older types of insulin than with the newer insulin analogues, and that titration regimens more closely mirror endogenous physiologic insulin and help decrease the incidence of hypoglycemia.²¹ In addition, insulin is often given at doses insufficient to achieve maximum benefit, despite the fact that insulin has no upper dose limit and higher doses result in better glucose measures.⁵

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Triple oral therapy is often a valid therapeutic option for patients whose fears of injections and/or hypoglycemia are a significant barrier to insulin therapy. However, the efficacy of adding a third OAD remains uncertain, particularly when baseline A1C levels are >9.0% and the maximum reduction in A1C shown with triple therapy has been 1.4% to 1.7%.^{22,23} Moreover, a recent study (N = 217) reported that basal insulin therapy (insulin glargine) combined with 2 OADs (a sulfonyleurea plus metformin) resulted in similar or greater reductions in A1C than did the addition of a third OAD (rosiglitazone) in oral therapy alone.²⁴ At week 24 of this study, A1C improvements from baseline were similar overall in both groups (–1.7% vs –1.5%), but the insulin glargine–treated group showed significantly greater improvement in patients with baseline A1C values >9.5% ($P < 0.05$). In this study, insulin glargine was associated with a

higher incidence of hypoglycemia but less weight gain than rosiglitazone.

For patients experiencing inadequate glycemic control with OADs alone, a relatively simple treatment approach is to initiate insulin therapy using once-daily basal insulin in combination with the previously prescribed oral regimen. The basal insulin dose is titrated on a regular schedule until glycemic targets are achieved. **Table II** provides a summary of currently available insulins and insulin analogues.^{25–27} Intermediate- or long-acting formulations are used for basal insulin therapy (eg, once- or twice-daily neutral protamine Hagedorn [NPH] insulin or insulin detemir, or once-daily insulin glargine).^{25,28}

Ease of use, efficacy in reaching glycemic goals, and risk of hypoglycemia are all important considerations in selecting an appropriate treatment regimen for patients initiating basal insulin therapy. The Treat-to-Target Trial²⁹ directly compared the efficacy and risk of hypoglycemia associated with once-daily NPH with those associated with insulin glargine when added to OAD therapy in 756 overweight patients whose type 2 DM was inadequately controlled (A1C >7.5%) with 1 or 2 OADs. This study used a forced titration algorithm (starting at 10 IU/d of basal insulin and adjusting weekly, seeking a target FPG ≤100 mg/dL). After 24 weeks, the mean A1C was similar between the insulin glargine and NPH groups (6.96% vs 6.97%), with ~60% of patients in each group achieving A1C levels ≤7.0%. However, significantly more patients in the insulin glargine group achieved this

level of glycemic control without a documented episode of nocturnal hypoglycemia (33.2% vs 26.7%, respectively; $P < 0.05$) and with decreased overall hypoglycemia.

In addition, the Glycemic Optimization with Algorithms and Labs at Point of Care trial³⁰ reported that active titration of insulin glargine according to a simple algorithm (similar to that described earlier) in a predominantly primary care setting resulted in significant improvements in glycemic control ($P < 0.001$) for patients with type 2 DM ($N = 7893$), with low rates of moderate and severe hypoglycemia (0.69 and 0.14 events/patient-year, respectively). Similarly, a comparison study of 2 different titration algorithms for insulin glargine reported that a simple patient-driven algorithm ($n = 2493$) significantly improved glycemic control in patients with type 2 DM without increasing severe hypoglycemia, versus a clinic-driven algorithm ($n = 2468$) ($P < 0.001$).³¹ In the patient-driven algorithm, the dose was increased by 2 IU/d every 3 days when mean fasting blood glucose (FBG) levels were ≥120 mg/dL (or 0–2 IU/d at the discretion of the physician for FBG levels 100–120 mg/dL). This study confirmed that dose titration of basal insulin therapy with insulin glargine can be safely and effectively managed by patients in general clinical practice settings.

In a further comparison of basal insulin therapy using insulin glargine versus NPH insulin in patients with type 2 DM ($N = 695$), treatment with once-daily (morning) insulin glargine plus glimepiride resulted in significantly better glycemic control than treatment with once-daily NPH insulin (bedtime) plus glimepiride (A1C improvement, -1.24% vs -0.84% ; $P = 0.001$).³² This study also reported a lower risk of nocturnal hypoglycemia with either morning (17%) or bedtime insulin glargine (23%) than with bedtime NPH insulin (38%) ($P < 0.001$). In another study of patients with type 2 DM ($N = 518$), insulin glargine was associated with less weight gain than NPH.³³ Moreover, when added to insulin therapy, metformin was associated with less weight gain

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Table II. Action profiles of insulins and insulin analogues available for prandial and basal insulin therapy.^{25–27}

Insulin Type	Onset	Peak	Duration
Rapid-acting analogues			
Glulisine/aspart/lispro	5–15 minutes	30 minutes–1.5 hours	4–6 hours
Short-acting			
Human regular	30–60 minutes	2–3 hours	8–10 hours
Inhaled insulin*	30–60 minutes	30 minutes–1.5 hours	3–6 hours
Intermediate-acting			
Human NPH	2–4 hours	4–10 hours	12–18 hours
Long-acting analogues			
Detemir	0.8–2 hours	Slight peak at 6–8 hours	Up to 24 hours
Glargine	2–4 hours	No pronounced peak	~24 hours

NPH = neutral protamine Hagedorn.

*Inhaled dry human insulin powder.

than placebo (mean, 6.1 vs 7.6 kg; adjusted difference, 1.5 kg [95% confidence difference, 0.5% (0.1–0.9)]; $P = 0.02$).³⁴

Another 2 studies^{35,36} compared insulin glargine basal therapy with premixed insulin formulations, demonstrating somewhat varying outcomes. Janka et al³⁵ concluded that adding once-daily insulin glargine to oral therapy with glimepiride plus metformin was safer and more effective than using twice-daily premixed 70% NPH/30% regular human insulin as monotherapy ($N = 371$; mean change in A1C, -1.64% vs -1.31% , respectively [$P < 0.001$]; A1C $\leq 7.0\%$ without confirmed nocturnal hypoglycemia, 45.5% vs 28.6% , respectively [$P < 0.002$]). In contrast, Raskin et al³⁶ reported that treatment with twice-daily biphasic insulin aspart 70/30 (209 patients completed the study) was more effective than insulin glargine in achieving glycemic goals (A1C $< 7.0\%$, 66% vs 40% ; $P < 0.001$), although more patients in the 70/30 group reported hypoglycemic episodes with plasma glucose levels < 56 mg/dL (43% vs 16% , respectively; $P < 0.05$). Important differences exist between these 2 studies that make side-by-side comparisons difficult. Baseline A1C values were higher in the study by Raskin et al ($\sim 9.7\%$, compared with 8.8% in the study by Janka et al), suggesting a need for the addition of prandial insulin to basal therapy in the insulin glargine-treated patients. In addition, previous sulfonylureas were replaced with glimepiride in the study by Janka et al, whereas in the study by Raskin et al, secretagogues and α -glucosidase inhibitors were discontinued.

In another study,³⁷ twice-daily insulin detemir was compared with NPH insulin in patients with type 2 DM ($N = 476$). At 24 weeks, both treatments produced similar reductions in A1C (from 8.6% to 6.7% and from 8.5% to 6.6% for insulin detemir and NPH, respectively), with a greater proportion of patients who used insulin detemir achieving these values without hypoglycemia (26% vs 16% , respectively; $P < 0.008$).

Although the addition of basal insulin therapy to OADs is an effective antihyperglycemic strategy, new classes of drugs have become available recently that can be used when oral agents alone no longer suffice. Exenatide, a mimetic of the incretin hormone glucagon-like peptide-1, is a noninsulin therapy injected twice daily at mealtimes. This agent is approved for use as adjunctive therapy in patients with type 2 DM whose disease is inadequately controlled with metformin, a sulfonylurea, a TZD, or a combination of metformin and a sulfonylurea or a combination of metformin and a TZD. Exenatide functions by enhancing glucose-dependent insulin secretion, reducing glucagon release, and slowing gastric emptying.³⁸ Exenatide has an advantage, particularly for obese patients, because it promotes satiety and typically is associated with weight reduction.³⁹ Similar to oral therapy, exenatide generally can be expected to reduce A1C levels by $\sim 1.0\%$ to 2.0% .^{38–41} Additionally, long-term effects of exenatide that increase first-phase insulin secretion in patients with type 2 DM have recently been reported.⁴²

Studies in which exenatide was added to a sulfonylurea with or without metformin showed a reduction from base-

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line to week 30 by $\sim 1.0\%$, and this reduction was sustained during an 82-week, open-label extension trial.^{43,44} In a study directly comparing the effects of exenatide versus insulin glargine when added to combination therapy with metformin plus a sulfonylurea, both treatments reduced A1C levels by 1.1% (from $\sim 8.2\%$ at baseline to 7.1% after 26 weeks).³⁸ The mean weight change was -2.3 kg in the exenatide group and 1.8 kg in the insulin glargine group; the most commonly reported adverse events were increased nausea, vomiting, and diarrhea in the exenatide group.³⁸

In addition to incretin mimetics, pramlintide also has been introduced recently for the adjunctive treatment of both type 1 and type 2 DM. This agent is a synthetic analogue of amylin, a 37-amino acid neurohormone that is secreted with insulin in response to meals, lowering serum glucose levels by reducing the release of glucagon, slowing gastric emptying, and reducing food intake. Pramlintide is approved for use by patients with type 2 DM who are using insulin at mealtimes only or in combination with metformin plus sulfonylurea therapy.⁴⁵ In studies of patients with type 2 DM, pramlintide reduced A1C levels by 0.3% to 0.6% , 1-hour PPG by 86.5 mg/dL, and 2-hour PPG by 61.25 mg/dL.⁴³ The most common adverse events in these trials were nausea and hypoglycemia; it is recommended that the premeal insulin dose be reduced by 50% when initiating therapy with pramlintide.

Patient Follow-Up After 6 Months of Treatment: Elevated Postprandial Glucose Levels

At the 6-month follow-up visit, E.L.'s weight remained essentially unchanged (262 lb), but his blood pressure ($126/72$ mm Hg) and lipid parameters (LDL-C, 92 mg/dL; HDL-C, 46 mg/dL; TG, 142 mg/dL) were all now within recommended target levels. With the addition (3 months earlier) of basal insulin glargine to his previously prescribed oral therapy (metformin plus sulfonylurea), he was now very close to the ADA-recommended target for A1C: his A1C level had decreased from 7.8% at his previous visit to 7.1% at the current visit. However, his plasma glucose levels—particularly his PPG levels—remained somewhat elevated. For the previous 2 weeks, his SMBG values were consistently > 100 mg/dL, ranging from a morning FPG of ~ 130 mg/dL to an evening PPG of ~ 180 mg/dL. Therefore, his new treatment plan included the following: maintain current dosages of metformin, glimepiride, pravastatin, lisinopril, hydrochlorothiazide, levothyroxine, and ASA; maintain insulin glargine at his current dosage of 60 IU/d (at bedtime); and add prandial insulin to his evening meal to control PPG excursions (insulin glulisine initiated at 1 IU/3 g carbohydrate before evening meal [this dosage to be

increased by 2 IU twice per week until his mean prebedtime blood glucose was 140 mg/dL). He was also scheduled for a 9-month follow-up visit.

Treatment Strategies

Although A1C levels are the primary target for glycemic control, PPG levels can contribute significantly to overall hyperglycemia—particularly in patients with lower A1C values. In patients with A1C values <7.3%, elevated PPG levels account for ~70% of the overall diurnal hyperglycemia.⁴⁶ It is now better recognized that elevations in PPG still can result in a significant risk for comorbidities despite adequately controlled FPG levels and near-target A1C values. An elevated 2-hour PPG level has been associated with increased microvascular complications such as nephropathy and retinopathy, as well as increased risk of death from cardiovascular disease.^{47,48} In fact, postprandial hyperglycemia (>140 mg/dL) in the presence of normal FPG (<110 mg/dL) and normal A1C values (<6.1%) have been associated with a 2-fold increased mortality risk from cardiovascular disease.⁴⁷

In patients already receiving basal insulin therapy, prandial insulin can be added, if necessary, using either short-acting (regular human) insulin or a rapid-acting insulin analogue (insulin aspart, lispro, or glulisine). Regular human insulin has a longer time to onset of action and a longer half-life than the rapid-acting analogues (Table II^{25–27}), thus requiring dosing ~30 minutes before meal intake to ensure adequate efficacy immediately postmeal and to avoid hypoglycemia a few hours after a meal.^{25,49} Rapid-acting analogues, in contrast, allow greater flexibility with their faster onset and shorter duration of action, permitting either pre-meal or postmeal dosing for individuals with unpredictable meal schedules.⁵⁰ A basal-prandial treatment regimen of insulin detemir and the rapid-acting analogue insulin aspart was shown to be as effective as NPH insulin in combination with mealtime regular human insulin in patients with type 2 DM, albeit 69% of the patients required twice-daily dosing of insulin detemir.⁵¹ A study comparing basal-prandial insulin regimens using either regular human insulin/NPH insulin or the insulin analogues insulin lispro and glargine in patients with type 1 DM demonstrated that the insulin analogue regimen significantly improved overall glycemic control by the end of the treatment period at 16 weeks (mean A1C, 7.5% vs 8.0%; $P < 0.001$).⁵² Another study used a simple algorithm targeting preprandial glucose in patients with uncontrolled type 2 DM.⁵³ The goal was to demonstrate that titrating mealtime doses of insulin glulisine with combination daily insulin glargine was as effective as adjusting glulisine according to carbohydrate counting in reducing A1C values and symptomatic hypoglycemia (<50 mg/dL). Consequently, a single dose of prandial insulin administered with the largest meal of the day, rather than the multiple daily injection regimens required for patients with DM, may be sufficient to control PPG excursions and achieve overall glycemic goals.

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As noted earlier, PPG is an important contributor to overall glycemic control.⁴⁶ Thus, PPG excursions may be driving up overall glucose levels in a patient who is receiving basal insulin and whose A1C level is above goal despite adequate dose titration. Performing SMBG can help determine if these PPG excursions are more pronounced during particular meals or times of day.

Patient Follow-Up After 9 Months of Treatment: Achievement of Glycemic Targets

At his 9-month follow-up visit (3 months after the addition of prandial insulin to his evening meal and his basal insulin therapy), E.L. showed an increase in body weight (to 264 lb), maintenance of blood pressure (124/73 mm Hg) and lipid parameters (LDL-C, 89 mg/dL; HDL-C, 48 mg/dL; TG, 132 mg/dL) below ADA-recommended targets, and a considerably improved glycemic profile. His A1C was now within the normal range (6.1%), and his 2-week SMBG values were consistently <100 mg/dL, ranging from a morning FPG of ~95 mg/dL to an evening PPG of ~147 mg/dL. The patient had experienced 2 mild episodes of hypoglycemia (blood glucose, 67 and 69 mg/dL) during the past month, both of which occurred during prolonged physical activity in the morning. He was advised at this point to reduce the evening insulin glargine dose by 2 IU each week until FPG values are >70 mg/dL. He also was advised to continue exercising and monitoring his diet and to maintain the same dosages of blood pressure medication, statin therapy, levothyroxine, ASA, OADs (metformin plus glimepiride), and insulin glulisine (currently at 28 IU before his evening meal).

The patient in this longitudinal case study reached all glycemic control targets by using combination therapy with 2 OADs plus insulin analogues (both basal and prandial therapy at 1 meal per day). At this point, continued aggressive treatment of hypertension and dyslipidemia, as well as continued long-term insulin therapy, were recommended.⁵

CONCLUSIONS

A key factor in this case patient's ability to reach glycemic targets within 1 year of diagnosis of type 2 DM was the accelerated implementation of insulin therapy. Such a therapeutic approach obviates the risk for uncontrolled hyperglycemia, which is associated with the standard practice of beginning treatment with diet and exercise alone and slowly advancing by 1 OAD at a time, ending with insulin therapy as a last resort. As illustrated in this case review, therapy can begin immediately with 2 OADs and be advanced to once-daily basal insulin administration after 3 months if glycemic targets are not met. After an additional 3 months, the addi-

tion of prandial insulin to the largest meal of the day can result in optimal control of postprandial glucose elevations. This is a simple, flexible, stepwise approach to advancing insulin therapy as needed in patients with type 2 DM. Given the well-known effect of unchecked hyperglycemia on the development of DM-related complications, the timely advancement of therapy should not be delayed in patients who are failing to reach glycemic targets.

ACKNOWLEDGMENTS

Editorial support was provided by Embryon Inc. (Somerville, New Jersey).

The author has received research grant funding from the following industries: Bayer Corporation (Elkhart, Indiana), Eli Lilly and Company (Indianapolis, Indiana), King Pharmaceuticals, Inc. (Bristol, Tennessee), and sanofi-aventis (Bridgewater, New Jersey).

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