CLINICAL DECISIONS
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Management of Type 2 Diabetes

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at www.nejm.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 55-year-old woman with type 2 diabetes, obesity, and hypertension has been under your care for the past 2 years. She has no history of microalbuminuria, retinopathy, or neuropathy. She has never had a cardiovascular event and reports no cardiac symptoms.

In the past, she has successfully lost weight (from 5 to 12 kg) on various diets but each time has regained all of the weight she lost. She tries to walk 30 minutes each day. She monitors her fasting glucose levels three times weekly using a personal glucometer, and her morning fasting glucose levels have ranged between 110 and 140 mg per deciliter (6.1 and 7.8 mmol liter). She has been receiving metformin (1000 mg twice a day) and glipizide (10 mg twice daily).

She has hypertension that is treated with hydrochlorothiazide (25 mg daily) and lisinopril (20 mg daily). She takes aspirin (81 mg daily) and simvastatin (20 mg daily). She notes that she consistently takes her medications.

She has a family history of cardiovascular disease with early stroke. On physical examination, her body-mass index (the weight in kilograms divided by the square of the height in meters) is 31. Her blood pressure is 128/78 mm Hg. Her general assessment, including cardiorespiratory, abdominal, and neurologic examinations, is normal.

Her glycated hemoglobin level is 8.1%, and her creatinine 0.9 mg per deciliter (80 mmol per liter). She has no microalbuminuria, and liver-function studies are normal. She seeks advice about the management of her diabetes.

Which one of the following treatment options, any one of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your past experience, recent guidelines, and other sources of information, as appropriate.

1. **Add pioglitazone.**
2. **Add neutral protamine Hagedorn (NPH) insulin before bedtime.**
3. **Add exenatide twice daily.**

To aid in your decision making, each of these approaches to treatment is defended by an expert in the management of diabetes in the following short essays. Given your knowledge of the condition and the points made by the experts, which treatment approach would you choose? Make your choice on our Web site (www.nejm.org).

TREATMENT OPTION 1

Add Pioglitazone

Ronald B. Goldberg, M.D.

The case vignette illustrates a key therapeutic decision most physicians face when managing type 2 diabetes: namely, how to advance treatment in patients whose glycated hemoglobin levels remain above the target value despite dual oral antihyperglycemic therapy, such as with metformin and glipizide, as in this patient. Medications such as pioglitazone can delay the almost inevitable necessity of initiating the use of insulin in such patients. Furthermore, patients receiving a thiazolidinedione who later need insulin may have a better response to it than those not receiving a thiazolidinedione. However, there are no comparative data to determine what the optimal treatment should be when a patient does not have

a response to dual oral therapy. I believe the addition of pioglitazone is a rational next step.

Several short-term trials have examined the effects of thiazolidinedione treatment as an "add-on" therapy in patients with elevated glycated hemoglobin values who are already taking maximum doses of metformin and a sulfonylurea. Collectively, these studies demonstrate that the addition of a thiazolidinedione can lower the glycated hemoglobin level by as much as 2 percentage points. Three such studies compared the addition of a thiazolidinedione or insulin to the metformin–sulfonylurea treatment regimen of subjects with baseline glycated hemoglobin values of more than 9.0%.[1-3] These studies showed that a thiazolidinedione had an efficacy similar to that of insulin in lowering glycated hemoglobin levels. Together, the studies suggest that, as compared with treatment with insulin, treatment with pioglitazone is associated with a lower incidence of hypoglycemia, a similar amount of weight gain, and an increase in the high-density lipoprotein (HDL) cholesterol level. The expenses associated with the triple oral therapies that include a thiazolidinedione are greater than those of either insulin (70% NPH insulin and 30% regular insulin) or insulin glargine added to metformin–sulfonylurea.[2,3]

Pioglitazone is likely to have few side effects and can be taken once daily. The weight gain that typically accompanies its use (3–4 kg, on average) can be mitigated by intensifying medical nutrition therapy at the time of initiation. Since recent evidence suggests that the use of thiazolidinediones may reduce bone density, a bone-density scan may be appropriate, particularly for women who are already postmenopausal.

It is possible that the need for initiating insulin therapy is delayed by the addition of pioglitazone in patients whose diabetes is inadequately controlled with the use of metformin and sulfonylurea. One study, A Diabetes Outcome Progression Trial (ADOPT), showed that rosiglitazone, when used as initial monotherapy in patients with a recent diagnosis of type 2 diabetes, maintained glycemic targets for longer than did treatment with sulfonylurea or metformin and suggested that this might be due to a beneficial effect on beta-cell function. Though the addition of pioglitazone to a regimen of metformin and a sulfonylurea could be expected to have a durable effect on the maintenance of improved glycemic control, especially if administered soon after the glycated hemoglobin level begins to rise, longer-term studies are needed to evaluate the effectiveness of this approach.

In support of this strategy, the ratio of proinsulin to insulin, considered a marker of beta-cell function, improved when pioglitazone was added to metformin and sulfonylurea as treatment.[4] Pioglitazone also mobilizes fat from the liver, an effect that is thought to be accompanied by sensitization of the liver to insulin. Fatty liver is common in patients with diabetes and is linked in selected patients to the development of steatohepatitis, which pioglitazone has been shown to ameliorate.

Finally, despite the findings in meta-analyses that rosiglitazone may increase the risk of ischemic events, a similar effect has not been demonstrated for pioglitazone.[5] In fact, there is evidence that treatment with pioglitazone increases the HDL cholesterol level by 10 to 15%, lowers the systolic blood pressure by 4 to 5 mm Hg, and reduces the thickness of the carotid wall, as compared with a sulfonylurea. In addition, a marginally beneficial effect on ischemic events was found when pioglitazone was added to existing treatment in patients with type 2 diabetes in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), a randomized, double-blind, controlled clinical trial of a strategy that was considered cost-effective. In combination, these results support the possibility that pioglitazone may have cardioprotective effects; it would be my choice for this patient.

Dr. Goldberg reports receiving speaker's honoraria from both Takeda and GlaxoSmithKline and consulting fees and grant support from Takeda. No other potential conflict of interest relevant to this article was reported.

From the Division of Endocrinology, Diabetes, and Metabolism, Diabetes Research Institute, University of Miami Miller School of Medicine, Miami.

TREATMENT OPTION 2

Add NPH Insulin before Bedtime

Rury Holman, F.R.C.P.

The case vignette of a patient with type 2 diabetes who has suboptimal glycemic control despite receiving maximum-dose oral therapy with met-

formin and a sulfonylurea is all too familiar. It reflects the progressive nature of the condition, in which declining beta-cell function results in elevations in glycemia year after year[6] unless antidiabetes medications are added or the doses of these medications are increased. In this obese patient who has no clinical evidence of complications from diabetes and whose cardiovascular risk factors are currently well managed, the immediate concern is the need to reduce the glycated hemoglobin level to below that recommended in the International Diabetes Federation 2005 guidelines (6.5%) to minimize the risk of future complications. Ideally, glycemic control should be handled in a proactive manner, according to the joint consensus algorithm for the management of hyperglycemia from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),[7] which suggests that a glycated hemoglobin value of 7% or more should serve as "a call to action to initiate or change therapy, with the goal of achieving a glycated hemoglobin level as close to the nondiabetic range as possible."

Adding a third oral agent is not recommended, given that the patient already has a glycated hemoglobin value of 8.1% and that this approach is relatively more expensive and potentially not as effective in reducing glycemia as adding insulin would be.[7] Adding a basal insulin to existing oral therapy has been shown to be more effective in reducing glycated hemoglobin levels than adding a thiazolidinedione — especially at higher initial glycated hemoglobin values — with less weight gain, no edema, salutary lipid changes, and a lower cost.[3] Indeed, the increased risk of edema, congestive heart failure, and fractures in women now recognized to be associated with thiazolidinediones and the uncertainty about their effects on the risk of cardiovascular disease have led to an updated recommendation by the ADA–EASD that greater caution should be exercised in their use. Adding exenatide in this patient would be unlikely to achieve the target glycated hemoglobin levels (<6.5% or <7.0%), given an expected absolute decrease in the level of only 0.5 to 1.0%, despite the potential weight loss, and would incur a risk of gastrointestinal side effects.[7] Also, exenatide requires twice-daily injections, and despite its increasing use, there have been no large-scale trials to assess its efficacy or safety in the long term.

Insulin therapy can reduce absolute glycated hemoglobin values sufficiently — by 1.5 to 3.5% — to allow glycemic targets to be met.[7] Adding an intermediate-acting insulin before bedtime is a relatively straightforward approach to increasing therapy for glycemia. It can be undertaken readily in a community-care–based setting and obviates the need to amend existing therapy. Some patients may be concerned about self-injection but can be reassured that with modern needles it is a virtually painless process and certainly much less onerous than their finger-stick capillary-glucose measurements. Maintaining existing sulfonylurea therapy when supplementing basal insulin requirements means that the required insulin dose is lower[8] and the problem of offsetting sudden glycemic deterioration when a sulfonylurea is withdrawn can be avoided.[9] The initiation of NPH insulin at bedtime involves a single injection at a time when patients will be undressed and does not require them to carry insulin-injection equipment during the day. Glycemic control can still be monitored, and the need for insulin-dose adjustments can be determined by continuing to measure mainly fasting glucose levels.

The Treat-to-Target trial showed that systematic titration of bedtime NPH insulin, used in addition to oral therapy, can safely achieve a 7% glycated hemoglobin value in a majority of overweight patients with type 2 diabetes who have glycated hemoglobin levels between 7.5% and 10.0% when receiving oral agents alone. The mean (±SE) weight gain was modest (2.8±0.2 kg) with a confirmed rate of hypoglycemic events of 5.1 per patient per year. The Treating to Target in Type 2 diabetes (4-T) trial showed that adding a basal insulin, instead of a biphasic insulin twice a day or a short-acting insulin three times a day, to metformin and sulfonylurea reduced the likelihood of hypoglycemia by half to three quarters, with a decrease in weight gain by half to two thirds. Insulin doses vary considerably among patients, but safe starting doses can be easily calculated, as shown in the 4-T trial. Patients can then adjust their doses, using a simple algorithm, as demonstrated in the Treat-to-Target trial. In the long term, this incremental approach to adding insulin therapy as a once-daily bedtime injection can ease the transition to a more complex insulin regimen in the face of continued hyperglycemic progression.

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From the University of Oxford, Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, United Kingdom.

TREATMENT OPTION 3

Add Exenatide Twice Daily

Daniel J. Drucker, M.D.

The management options for the treatment of type 2 diabetes have become more complex since the introduction of several new classes of drugs and emerging data about the safety and efficacy of older drugs. It remains difficult to predict the response to specific therapies targeting different antidiabetes mechanisms, and all three options posed in the case vignette are reasonable and efficacious. There are no available head-to-head trials that have directly compared the efficacies of pioglitazone, NPH insulin, and exenatide in patients in whom glycemic control has not been achieved with the use of metformin and a sulfonylurea; thus, it seems reasonable to make clinical decisions on the basis of available data. The addition of pioglitazone will improve insulin sensitivity and glucose control but probably will be associated with fluid retention and weight gain and an increased risk of osteoporosis.[10] Insulin therapy, while effective, may also be associated with weight gain and a need for more frequent glucose monitoring to minimize the risk of hypoglycemia.

Two new classes of antidiabetes agents based on the potentiation of incretin action have been approved for the treatment of type 2 diabetes: the glucagon-like peptide 1 (GLP-1) receptor agonists, exemplified by exenatide, and the dipeptidyl peptidase IV inhibitors that include sitagliptin and vildagliptin[11]; other drugs are currently in clinical trials. Exenatide (as well as GLP-1) lowers blood glucose levels by stimulating insulin secretion and inhibiting glucagon secretion. These drugs also appear to inhibit gastric emptying and enhance satiety, leading to weight loss in a substantial number of patients.

A recent meta-analysis of clinical trials involving incretin therapies concluded that the efficacy of these agents was generally similar to that of other antidiabetes therapies. Of direct relevance to the treatment of this patient, exenatide produces more potent control of postprandial glycemia than NPH insulin or pioglitazone, probably because exenatide suppresses gastric emptying. This finding may be important, in view of data linking the control of postprandial glycemia to cardiovascular risk in patients with diabetes. The opportunity to improve postprandial glucose control, while achieving weight loss, is appealing.

Although considerable preclinical data suggest that GLP-1–receptor agonists improve beta-cell function and are cardioprotective, such discussions may not be directly relevant for the care of this patient. The actions of GLP-1–receptor agonists on the stimulation of insulin and inhibition of glucagon secretion are glucose-dependent; hence, there is a very low risk of hypoglycemia in the absence of concomitant sulfonylurea therapy. The remarkable ability of GLP-1–receptor agonists to improve the glucose sensitivity of beta cells and potentiate insulin secretion rapidly suggests that discontinuation of the glipizide (or alternatively, the initial reduction of the dose by 50%), coincident with initiation of exenatide therapy, would be prudent.

The addition of exenatide to ongoing metformin and sulfonylurea therapy was associated with an absolute reduction of 0.8 to 1.0% in the glycated hemoglobin level, with 0.9 to 1.6 kg of weight loss, after 30 weeks of therapy in subjects with type 2 diabetes.[12] There have been several head-to-head comparisons of regimens of insulin administration, as compared with twice-daily exenatide, in patients who did not have adequate glycemic control when they were taking metformin and a sulfonylurea.[13,14] The use of exenatide and the use of insulin resulted in similar degrees of reduction in glycated hemoglobin and similar numbers of hypoglycemic events, but the resultant body weight was significantly higher at the end of the study in patients receiving insulin, often as much as 4 kg higher than in subjects taking exenatide.

What are the potential limitations associated with exenatide therapy? Gastrointestinal side effects, principally nausea, generally abate several weeks after the initiation of exenatide therapy.

Nausea and gastrointestinal upset may limit tolerability in 10 to 20% of patients, and pancreatitis has recently been described in subjects treated with exenatide, although the actual prevalence is low and the pathophysiological characteristics remain uncertain. Exenatide therapy is expensive, and its long-term durability and safety have not been defined. Since incretin drugs are new, they are comparatively more expensive than older agents, and we do not yet have outcome studies to determine the long-term effects of exenatide on beta-cell function or cardiovascular events. On the other hand, the use of exenatide reduces glycemia through multiple mechanisms of action, is simple to use, and provides superior control of postprandial glucose. Critically, unlike with existing diabetes therapies, many subjects will experience satiety and weight loss. These features make exenatide an appealing option for the treatment of patients in whom existing antidiabetic agents fail to achieve glycemic control.

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From Banting and Best Diabetes Centre, University of Toronto, Mount Sinai Hospital, Toronto.

1. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004;116:230-5.
2. Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P, INS-2061 Study Team. Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. Diabetes Care 2003;26:2238-43.
3. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29:554-9.
4. Dorkhan M, Magnusson M, Frid A, Grubb A, Groop L, Jovinge S. Glycaemic and nonglycaemic effects of pioglitazone in triple oral therapy of patients with type 2 diabetes. J Intern Med 2006;260:125-33.
5. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180-8.
6. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16: overview of six years' therapy of type 2 diabetes: a progressive disease. Diabetes 1995;44:1249-58. [Erratum, Diabetes 1996;45:1655.]
7. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2006;29:1963-72. [Erratum, Diabetes Care 2006;49:2816-8.]
8. Holman RR, Steemson J, Turner RC. Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement. Diabet Med 1987;4:457-62.
9. Nybäck-Nakell Å, Adamson U, Lins PE, Landstedt-Hallin L. Glycaemic responsiveness to long-term insulin plus sulphonylurea therapy as assessed by sulphonylurea withdrawal. Diabet Med 2007;24:1424-9.
10. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab 2006;91:3349-54.
11. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705.
12. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28:1083-91.
13. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2005;143:559-69.
14. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 2007;50:259-67.