



Council for the Advancement of Diabetes Research and Education

MISSION STATEMENT

CADRE is a nonprofit organization committed to reducing the burden of diabetes by providing health care professionals with scientific information and educational initiatives designed to translate research into effective clinical practice.

CADRE'S "DIABETES TACTICS"

CADRE's "Diabetes Tactics" are case studies presenting challenging diabetes treatment scenarios that practitioners are likely to encounter. These brief case studies explore controversies or dilemmas in diabetes management and offer practical suggestions for dealing with management challenges. CADRE is pleased to partner with *Insulin* to provide these educational cases to readers of this journal.

This issue's "Diabetes Tactics" discussion is provided by Mazen Alsahli, MD, and John E. Gerich, MD, of the Department of Medicine, University of Rochester School of Medicine, Rochester, New York.

WHAT TO DO WHEN A PATIENT IS ON MAXIMAL DOSES OF METFORMIN AND A SULFONYLUREA AND STILL HAS UNSATISFACTORY GLYCEMIC CONTROL?

CASE PRESENTATION

A 60-year-old man had a routine insurance physical 4 years ago. At that time, he reported no major health problems. His blood pressure (BP) was 145/90 mm Hg, his height was 68 inches, and his weight was 180 lb (body mass index [BMI], 27.4 kg/m²). Laboratory test results were normal with the following exceptions: glycosylated hemoglobin (A1C), 7.4%; fasting plasma glucose (FPG), 142 mg/dL; triglycerides (TG), 300 mg/dL; low-density lipoprotein (LDL), 163 mg/dL; and high-density lipoprotein (HDL), 32 mg/dL.

The patient was told that he was overweight and that he had mild type 2 diabetes mellitus (DM), high BP, and high cholesterol. He was enrolled in a lifestyle modification program, including diet and exercise, and was started on metformin 500 mg twice daily, atorvastatin 10 mg once daily, aspirin 81 mg once daily, and lisinopril 10 mg once daily.

At 3-month follow-up, his weight was unchanged, BP was 130/85 mm Hg, TG was 200 mg/dL, LDL was 100 mg/dL, HDL was 36 mg/dL, A1C was 6.7%, and FPG was 105 mg/dL. He continued on metformin 500 mg twice daily. At the next 3-month follow-up visit, however, his A1C had increased to 7.3%. Because his A1C was still above normal (4.0%–6.0%) (CADRE recommendation: A1C as close to normal as possible without unacceptable hypoglycemia), his metformin was increased to 500 mg 3 times daily.

He failed to come to his next 2 scheduled follow-up visits. When he presented again 9 months later, he weighed 184 lb (BMI, 28 kg/m²), his A1C had increased to 7.8%, and his FPG was 130 mg/dL. His metformin was then increased to 1000 mg twice daily.

Three months later, his A1C (7.5%) was still above goal. He continued on metformin 1000 mg twice daily and was started on a sulfonylurea (glimepiride 2 mg once daily). At the next 3-month visit, his A1C was 7.1% (still above goal); his metformin regimen remained the same, but his glimepiride was increased to 4 mg once daily.

The patient continued on this combination therapy and was seen every 3 months over the next year. His A1C ranged between 6.2% and 6.8%. However, 3 months later, his A1C was 7.5%. His weight had increased to 191 lb (BMI, 29 kg/m²), but no other measurements had changed significantly. Therefore, his metformin regimen was not changed, but his glimepiride was increased to the maximum dosage of 8 mg once daily.

He missed another appointment and now, 6 months later, he weighs 195 lb (BMI, 29.6 kg/m²), his A1C is 8.4%, and his FPG is 145 mg/dL on maximal doses of metformin and the sulfonylurea (Table). What do you do?

	Diagnosis	+3 mo	+6 mo	+15 mo	+18 mo	+21 mo	+36 mo	Today (+42 mo)	
Weight, lb	180	180		184			191	195	
A1C, %	7.4	6.7	7.3	7.8	7.5	7.1	7.5	8.4	
FPG, mg/dL	142	105		130				145	
Diabetes medications (in addition to diet and exercise/ lifestyle modifications)	Metformin 500 mg BID	Metformin 500 mg BID	Metformin 500 mg TID	Metformin 1000 mg BID	Metformin 1000 mg BID	Metformin 1000 mg BID Glimepiride 2 mg QD	Metformin 1000 mg BID Glimepiride 4 mg QD	Metformin 1000 mg BID Glimepiride 8 mg QD	?

A1C = glycosylated hemoglobin; FPG = fasting plasma glucose; BID = twice daily; TID = 3 times daily; QD = once daily.

Analysis

This case represents a common scenario in type 2 DM in which the disease progresses and the treatment needs to be adjusted frequently to maintain adequate glycemic control. The patient has gained weight and his glycemic control is unsatisfactory despite maximal doses of metformin and glimepiride. Following the “3F” principle (fix the fasting first), his regimen should be intensified to target fasting hyperglycemia as a first step and then postprandial hyperglycemia should be addressed if his A1C is not at goal. Many options are available. According to guidelines developed by the American Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists, you could add a basal insulin, a thiazolidinedione (TZD), or exenatide.

Recommendations

After explaining the treatment options, the progressive nature of type 2 DM, and the advantages of weight loss to the patient, it was agreed that the patient would start basal insulin therapy (glargine 20 units at dinnertime) and enroll in a weight-loss program. He was instructed to increase his glargine by 2 units every 3 days until his FPG was consistently in the 90- to 100-mg/dL range. He was also instructed on how to reduce the dose if unexplained hypoglycemia occurred.

Rationale

According to clinical trials, basal insulin (glargine, neutral protamine Hagedorn [NPH], detemir) and predinner premixed insulin (70/30 or 75/25) would probably be equally efficacious in this patient, with glargine/detemir probably causing less weight gain and less risk of hypoglycemia than a premix and NPH. Glargine was preferred over detemir because it lasts 24 hours and has no peak in activity.

If the patient's A1C had been >9.0%, twice-daily premix or a basal-bolus regimen (with discontinuation of the sulfonylurea) probably would have been needed. In the future, as the patient's β -cell function inevitably deteriorates, some type of prandial insulin will be needed.

A TZD was not chosen because clinical trials show that in a patient such as ours, TZDs are not superior to 70/30 insulin, NPH, or glargine in reducing A1C, and they are more costly and produce comparable weight gain. Despite a lower risk of hypoglycemia, 2 studies (the PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive] and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes [RECORD] studies) indicate no unique cardiovascular benefit from TZDs. Other studies indicate increased risk of fractures, edema, and heart failure. Finally, as shown in the ADOPT study (A Diabetes Outcome Progression Trial), the differences in the annual rate of decline in β -cell function between a sulfonylurea (glyburide, 6.1%), metformin (3.1%), and a TZD (rosiglitazone, 2.0%) were clinically insignificant.

Neither a dipeptidyl peptidase-4 inhibitor nor an α -glucosidase inhibitor was chosen because no data are available on triple therapy with these agents; they preferentially target postprandial hyperglycemia and, based on studies of additions to metformin or a TZD, they would not be expected to be particularly efficacious in a patient with an A1C of 8.4%.

Exenatide, although associated with weight loss in contrast to the weight gain seen with insulin, was not chosen because it has not been shown to be more efficacious than insulin, would require 2 injections (instead of 1 injection of basal insulin), is associated with a risk of pancreatitis, and, finally, would be more expensive and less well tolerated due to gastrointestinal side effects (principally nausea). The risk of hypoglycemia with exenatide has been shown to be similar to that of glargine when either is added to a regimen of metformin and a sulfonylurea.

Key Messages

- Type 2 DM is a progressive disease (β -cell function diminishes over time). Therefore, most patients will ultimately require some form of insulin therapy to achieve optimal glycemic control.
- When maximal doses of 2 oral agents fail to achieve or maintain adequate glycemic control, adding a third oral agent is not cost-effective.
- For patients with type 2 DM who fail therapy with 2 oral agents and whose A1C is <9.0%, once-daily basal insulin is the simplest regimen—and is at least as effective as other injectable regimens.
- For patients with type 2 DM who fail therapy with 2 oral agents and whose A1C is \geq 9.0%, basal-bolus insulin or a twice-daily premixed insulin regimen is usually needed to achieve optimal control.

Outcome

At 3-month follow-up, the patient had lost 4 lb and had titrated his glargine up to 40 units per day. Similar to results in the Treat-to-Target Trial, his FPGs had decreased over the first month to 124 mg/dL and thereafter plateaued at 117 mg/dL.

His A1C was 6.9%. He had no severe hypoglycemic reactions, but once or twice a week felt low before lunch (lowest self-monitored blood glucose was 66 mg/dL). Consequently, diet therapy was reinforced and it was recommended that he increase the basal insulin to try to achieve an FPG between 90 and 100 mg/dL most of the time.

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RECOMMENDED READING

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