JAOA: Journal of the American Osteopathic Association
www.jaoa.org

J Am Osteopath Assoc **May 1, 2008** vol. 108 no. 5 suppl 3 **S14-S19**

Reducing Global Cardiovascular Risk in Patients With Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) and its complications must be managed by using a comprehensive, or global, approach to treatment. The author describes the case of a white man, aged 51 years, with T2DM that was diagnosed 3 years earlier. The patient was obese and had a history of chronic low back pain. He also had diagnosed hypertension, decreased vibratory sensation in the feet, an S4 atrial gallop, trace ankle edema, degenerative joint disease in the knees, and decreased range of motion in the lumbar spine. Other findings at the patient's initial visit included hyperglycemia, microalbuminuria, and lipid abnormalities. Initial treatment included metformin; a nonsteroidal anti-inflammatory drug (naproxen); a thiazolidinedione (rosiglitazone maleate); a thiazide diuretic (hydrochlorothiazide); an angiotensin-converting enzyme inhibitor (enalapril); and low-dose aspirin. At 6-month follow-up, the patient continued to have elevated glycosylated hemoglobin, hypertension, dyslipidemia, and excess weight. Additional treatment strategies consisted of pioglitazone hydrochloride; metformin in combination with the dipeptidyl peptidase IV inhibitor sitagliptin phosphate; a statin (atorvastatin hydrochloride); and enrollment in a diet and exercise program. Results at 12-month follow-up included a substantial decrease in glycosylated hemoglobin and improved hypertension and dyslipidemia. The patient was successfully treated across the full range of global cardiovascular risk reduction.

Without the many complications associated with type 2 diabetes mellitus (T2DM), this illness would lose much of its “sting.” It is crucial to effectively manage T2DM and its complications by using a comprehensive approach to treatment. Such a comprehensive, or global, approach needs to address hyperglycemia, hypertension, dyslipidemia, obesity and diet, physical inactivity, and smoking cessation. Furthermore, these issues need to be considered across the full spectrum of ethnicity, gender, and age.

A number of pharmacologic agents are available to target different pathophysiologic elements of T2DM in the hopes of generating improved outcomes in patients. These agents include α-glucosidase inhibitors (AGIs); angiotensin-converting enzyme (ACE) inhibitors; dipeptidyl peptidase IV (DPP-IV) inhibitors; hydroxymethylglutaryl-coenzyme A reductase inhibitors (ie, statins); incretin mimetics; metformin; nonsteroidal anti-inflammatory drugs (NSAIDs); sulfonylureas; and thiazolidinediones (TZDs).[1]

The goals of management for patients with T2DM include a glycosylated hemoglobin (HbA_{1c}) level of less than 7%, or generally as close to normal (≤6%) as feasible without precipitating such adverse events as hypoglycemia.[1-3] The blood pressure target for T2DM management is less than 130/80 mm Hg, or even lower if there are mitigating circumstances, such as the presence of renal disease. For the patient's lipid profile, a low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL is the target for both men and women.[4] The high-density lipoprotein cholesterol (HDL-C) target for men is greater than 40 mg/dL, and for women, greater than 50 mg/dL.[4] A triglyceride concentration of less than 150 mg/dL is desired for patients with T2DM.[1-4]

It is important to keep in mind that insulin resistance in general, and conditions characterized by insulin resistance (such as T2DM), are prothrombotic states. For

that reason, low-dose aspirin therapy is recommended—in the absence of any contraindications—as primary prevention for cardiovascular disease (CVD) in patients who are older than age 40 years and in others who have more than one risk factor for CVD.[5] In addition, it is vital to keep patients with T2DM away from smoking cigarettes.

Limits to Effectiveness of Current Treatments

When treatment targets for patients with T2DM are compared with actual treatment results achieved in the clinical setting, the "report card" on T2DM management outcomes is not encouraging.[6] Nearly two out of three patients being treated for T2DM have suboptimal glucose control. Only about 37% of patients under treatment for T2DM have achieved the conservative HbA_{1c} target of less than 7%.[6] Furthermore, another 37% of patients being treated for T2DM have HbA_{1c} levels greater than 8%.[6]

The results of the United Kingdom Prospective Diabetes Study (UKPDS)[7] indicated that for every 1% increase in HbA_{1c} level, there is a 14% increase in risk of myocardial infarction and a 37% increase in the risk of any diabetes-related complications. Thus, an HbA_{1c} level of 8% or greater represents an extremely dangerous CVD risk. The UKPDS results also suggested that only 36% of patients being treated for T2DM have adequate blood pressure control, and more than half of patients with T2DM have total cholesterol levels that are higher than targeted values.[7]

When all the risk factors that aggregate to accelerate macrovascular disease in people with T2DM are considered—including HbA_{1c}, blood pressure, and cholesterol levels—fewer than 10% of Americans under treatment for T2DM have reached targeted values for all those risk factors.[6]

Part of the reason for our poor "report card" on T2DM management is related to the fact that there are serious limitations in our current arsenal of treatment approaches. For example, many pharmacologic agents used in T2DM management have an inadequate duration of effect, not keeping patients' glycemic conditions under control for extended periods. As reported in the UKPDS,[7] after an initial reduction in blood glucose following treatment initiation, HbA_{1c} levels tend to drift back upward within a few years—a trend represented by the so-called "Nike curve of diabetes." Even with continued treatment, HbA_{1c} levels in many patients with T2DM begin to drift out of the goal range within 2 to 3 years.[7]

Other common problems that are associated with current treatments for patients with T2DM include risks of such adverse effects as hypoglycemia and gastrointestinal distress, as well as weight gain and edema.[8] In elderly patients, there are risks of renal impairment and congestive heart failure.[8] These are only a few of the limitations to current treatment approaches for patients with T2DM.

It is clear that a comprehensive multifactorial approach to treatment is needed as the standard of care for patients with T2DM to reduce the risk of vascular disease. We can no longer cherry-pick which CVD risk factor may be the most important, because all such factors contribute to accelerated macrovascular disease.

An increased array of antihyperglycemic therapies is needed to best tailor effective treatment regimens for the needs of individual patients. In addition, the combination of different therapies would ideally minimize such adverse effects as hypoglycemia and weight gain.

Pathophysiologic Considerations

It is important that treatment approaches for patients with T2DM be considered from the perspective of the underlying pathophysiologic factors. Most of the newer medications that have become available for T2DM and its complications make sense as treatments only to the degree that they address specific elements of the known pathophysiologic development of the disease.

For example, obesity is the main forerunner for most cases of T2DM. One of the hallmarks of obesity that gives it this association with T2DM is that it is an insulin-resistant condition. That is one problem. Another problem that drives the development of T2DM is the failure of β cells to adequately compensate for this insulin resistance. Most obese patients have adequate β-cell compensation for insulin resistance, and T2DM does not develop in these individuals. This fact is highlighted by statistics revealing the prevalence of obesity and overweight in the United States to be greater than 60%, yet the prevalence of T2DM is only about 7%.[9] Thus, it is clear that patients with T2DM have a combination of obesity related to insulin resistance *and* inadequate β-cell function. There is a genetic predilection for β-cell failure—and T2DM develops in individuals with this genetic predilection.

Another pathophysiologic abnormality that we must remain aware of is the fact that glucagon is secreted in excess in people with T2DM, and this hyperglucagonemia stimulates hepatic glucose production. Hepatic glucose production, in turn, is a major driver of increased fasting plasma glucose (FPG) levels. Patients with T2DM demonstrate a failure to suppress glucagon during meals—and this failure contributes to the insulin resistance in these patients.

Normal islet β cells can adapt to insulin resistance, which is why most overweight and obese patients do not have T2DM. However, a failure of this adaptation to insulin resistance can cause impairment of postprandial glucose disposal and subsequent impairment of fasting glucose. These two conditions, which are commonly seen in patients with prediabetes, result from a combination of defects in insulin secretion and a loss of islet β-cell mass. Patients with prediabetes also have a relative increase in glucagon levels, which contributes to the development of hyperglycemia and T2DM in these individuals.[1]

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Table

Examination and Laboratory Test Findings

Our Challenge

Effective glycemic control is the best-known strategy to reduce T2DM-associated morbidity and mortality.[1] However, despite the availability of a diverse arsenal of pharmacologic treatment agents—as well as insulin and insulin analogs—clinicians continue to struggle in balancing efficacy with adverse effects. In other words, the degree of desirable glucose lowering must often be balanced with such undesired conditions as hypoglycemia, weight gain, and edema.

This dilemma indicates that there is a great need for new therapeutic approaches with fewer limiting factors for patients with T2DM.

Case Presentation

The current case involves balancing global cardiovascular risk with glycemic control in a white man, aged 51 years, with T2DM that was diagnosed 3 years previously. The patient, Sam (not his real name), was a truck driver with a sedentary lifestyle. He was obese, with a weight of 225 lb, a height of 5 ft 9 in, a waist circumference of 46 in, and a body mass index (BMI) of 33. He reported a history of difficulty in losing weight, as well as chronic low back pain. His blood pressure was elevated, at 136/86 mm Hg, and his history included having hypertension for 10 years.

Sam's pertinent physical examination and laboratory findings at his initial visit are reported in the *Table*. His physical examination clearly revealed central obesity, ergo his large waist size. The examination also found acanthosis nigricans (ie, areas of thickened, hyperpigmented skin) on the neck and axillas. Sam had decreased vibratory sensation in his feet. A cardiac auscultation revealed an S4 (ie, atrial gallop sound). Other physical examination findings included trace ankle edema, degenerative joint disease in the knees, and some decreased range of motion in the lumbar spine.

Medications reported as being used by Sam for the 2 years prior to his initial visit included the following: metformin (2 g/d); an NSAID (naproxen, 220 mg twice/d); a TZD (rosiglitazone maleate, 4 mg/d); a thiazide diuretic (hydrochloro thiazide, 12.5 mg/d); an ACE inhibitor (enalapril, 20 mg/d); and low-dose aspirin (*Figure*).

The laboratory test results for Sam at his initial visit (*Table*) revealed an elevated level of FPG, at 160 mg/dL, and an HbA_{1c} level that was far out of the normal range, at 8.1%. His total cholesterol level was 197 mg/dL, with an LDL-C level of 118 mg/dL, an HDL-C level of 38 mg/dL, and a triglyceride concentration of 205 mg/dL. His albumin creatinine ratio was 36, above the normal value of less than 30. His creatinine level was 1 mg/dL. His liver function test results were normal.

A review of the Sam's physical examination and laboratory test findings showed that he was out of the normal ranges for many crucial aspects of his overall metabolic profile, consistent with the presence of cardiometabolic risk and metabolic syndrome, as defined by criteria of the National Cholesterol Education Program.[4] For example, his elevated FPG level was consistent with the presence of diabetes mellitus, and his abnormal total cholesterol, HDL-C, and triglyceride levels were indicative of CVD.

Clinical Considerations

The clinical considerations for Sam included hyperglycemia, hypertension, microalbuminuria (indicative of the beginning of renal insufficiency), lipid abnormalities and obesity, a sedentary lifestyle, and degenerative joint disease. These considerations implied the need for substantial therapeutic changes in the patient's lifestyle.

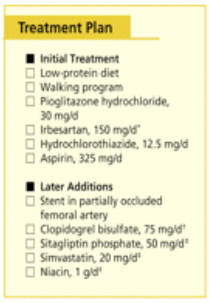

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Figure.

*Initial treatment plan, with subsequent additions, used for the patient. * Sitagliptin and metformin were taken as a combination pill. † Pioglitazone was used as a replacement for rosiglitazone because of patient's concerns regarding safety.*

Whether following guidelines from the American Diabetes Association,[1] the American Association of Clinical Endocrinologists,[3] or the International Diabetes Federation,[10] even the most conservative approach to the treatment of this patient means that his HbA_{1c} level needs to be reduced to less than 7%; his preprandial plasma glucose level, to 90 to 130 mg/dL; his postprandial plasma glucose level, to less than 180 mg/dL; and his blood pressure, to less than 130/80 mm Hg.

Many of the treatment algorithms that have been developed for patients with T2DM are designed to be decision trees based on the best clinical evidence, given the available pharmacologic agents.[2] These algorithms suggest that patients who have diagnosed T2DM should be initially placed on lifestyle intervention and metformin therapy. There has been an increasing realization that patients with T2DM rarely achieve glycemic goals by using lifestyle intervention alone.[2] If metformin is added to the treatment plan, however, chances of reaching glycemic goals are improved. When HbA_{1c} levels are successfully reduced below 7%, a patient can remain on a regimen of metformin with exercise, weight control, and medical nutrition programs. When HbA_{1c} levels stay above 7%, additional intervention is called for. Second-tier treatment would include sulfonylureas, a glitazone TZD, or initiation of insulin

therapy.[2]

If a patient's HbA_{1c} levels persist in being greater than 7%, the addition of a third oral antidiabetes agent may be desirable in some cases.[2] At this stage, however, it may be preferable to initiate more intensive insulin therapy for the patient.

With the range of treatment options available for patients with T2DM, each of the pathophysiologic problems can now be addressed—albeit with attendant risks for occasional adverse effects. Diet and exercise programs can lead to lower insulin resistance. Sulfonylureas can modulate the amount of insulin release from β cells by sensitizing the cells to glucose.[11] Incretin agents—which include both DPP-IV inhibitors (ie, sitagliptin phosphate) and incretin mimetics (eg, exenatide)—have a number of unique properties.[11,12] DPP-IV inhibitors inhibit the breakdown of naturally occurring glucagon-like peptide 1 (GLP-1), while incretin mimetics increase the amount of GLP-1 activity in the serum.

Although DPP-IV inhibitors and incretin mimetics differ in their modes of action, both can lower glucagon levels. Gastric emptying is affected most dominantly by exenatide. Thus, central effects on appetite and more pronounced effects on weight loss can be achieved with exenatide treatment.[13] The DPP-IV inhibitors, by contrast, are weight neutral.[11,12]

Biguanides are antidiabetes agents that function by suppressing production of hepatic glucose. The AGIs work by inhibiting absorption of carbohydrates. The TZDs can lower insulin resistance.

Interesting developments have recently been reported with regard to rosiglitazone, a TZD.[14,16] In A Diabetes Outcome Progression Trial (ADOPT),[15] researchers found that patients using rosiglitazone maintained the lowest HbA_{1c} levels during the 4-year study, compared with patients using either metformin or glyburide. Investigators with the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial[16] concluded that rosiglitazone substantially reduced incident T2DM and increased the likelihood of regression to normoglycaemia in adults with impaired fasting glucose and/or impaired glucose tolerance.

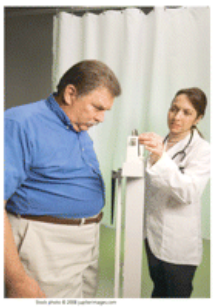
These and other findings on the effects of rosiglitazone in patient populations will allow more informed decisions to be made about the use of this medication. Pioglitazone, however, is currently a more commonly prescribed TZD than rosiglitazone for patients with T2DM.

Six-Month Follow-Up

Sam continued using the medication regimen reported in his initial visit (*Figure*) until his 6-month follow-up visit. He also attempted to add lifestyle modification to the management of his T2DM. At 6-month follow-up, Sam underwent laboratory tests again. The results of these tests are reported in the *Table*.

The laboratory test results revealed that Sam's hypertension and dyslipidemia were relatively well controlled, though his weight remained a problem. His total cholesterol level was 177 mg/dL, with an LDL-C level of 102 mg/dL and an HDL-C level of 36 mg/dL. His triglyceride concentration was 195 mg/dL. Despite the use of two oral glycemic agents, Sam's HbA_{1c} level was still out of the normal range, at 7.8%. His FPG level was 160 mg/dL (*Table*).

Glycemic control was a key focus of this patient's treatment—though the potential for adverse effects related to medication use had to be kept in mind. With each passing month, the health of Sam's β cells was deteriorating. Thus, additional treatment strategies were urgently called for.□



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Treatment Options

Various options were available for enhanced glycemic control in this patient. Making additional lifestyle changes, increasing doses of his current medications, and initiation of basal insulin, a DPP-IV inhibitor, or a GLP-1 analog (ie, incretin mimetic) were among these options. Each of these options is associated with certain expectations.

The initiation of basal insulin would have been the chosen prerogative of the clinician who expected the algorithm of Nathan et al[2] to be the best treatment guide. With the use of a DPP-IV inhibitor, the patient would be expected to benefit from additional lowering of his glucose levels, along with a low risk of adverse effects.[11,12] A DPP-IV inhibitor would be expected to produce decreases in the patient's FPG levels and postprandial glucose levels because of the suppression of glucagon and other beneficial effects of these medications.[11,12] A GLP-1 ana log would be expected to produce similar benefits, as well as possible augmentation of the patient's weight loss.[13] However, GLP-1 analogs are injectable medications that have a fairly robust adverse-effect profile.

Important factors in determining which kind of pharmacologic treatment to use for a patient with T2DM include the physician's long-term experience and comfort with a particular drug and the adverse-effect profile of that drug. A physician would want to use a medication that was weight neutral and that carried minimal risk of hypoglycemic events. Other factors that a physician might consider would be formulary access, cost, consistency with expert recommendations in guidelines and algorithms, and the likelihood that the patient would actually use the drug (ie, patient adherence).

DPP-IV Inhibitors

The DPP-IV inhibitors are potent reducers of glucagon secretion, and they help lower FPG levels and suppress hepatic glucose production and postprandial hyperglycemia.[11,12] Unlike the GLP-1 analogs, which affect satiety centers of the brain and contribute to weight loss, DPP-IV inhibitors are weight neutral.[11,12]

Sam had multiple features of metabolic syndrome, including inadequately managed FPG and triglyceride levels. He also had diagnosed trace edema and an S4 atrial gallop. It is important to treat patients like Sam with medications that carry low risks for serious adverse effects. Incretin enhancer agents, such as DPP-IV inhibitors, are not associated with increased risk for hypoglycemia, edema, or any other serious adverse effect.[11,12] The DPP-IV inhibitors have a benign risk profile for adverse effects.

Compared with sulfonylurea treatment, the expected effects of DPP-IV inhibitor treatment include a similar efficacy in lowering HbA_{1c} levels, a lower risk of hypoglycemia, and no additional weight gain.[11,12] Another benefit of using DPP-IV inhibitors is that they have a once-daily dosing schedule—making patient adherence to the treatment regimen more likely with DPP-IV inhibitors than with either short-acting sulfonylureas or exenatide, both of which may require multiple doses per

day.[11-13]

Additions to Treatment and Case Results

The various treatment options were discussed with Sam. Afterward, he expressed a favorable view toward the weight-loss potential of exenatide, but he noted that he was reluctant to use an injectable form of treatment. He also expressed concern regarding the safety of continuing rosiglitazone treatment, noting that he had recently read and heard unfavorable reports about rosiglitazone.[17] Because of this concern, the patient's TZD was switched from rosiglitazone to pioglitazone hydrochloride (30 mg/d).

Elements of Sam's revised treatment plan are shown in the *Figure*. He opted to receive the DPP-IV inhibitor sitagliptin phosphate (100 mg/d) together with metformin (1 g/d) in a combination pill at a dosage of 50/500 mg twice daily. The combination pill reduced the number of pills that he had to take every day, thereby improving the likelihood of patient adherence. Sam also agreed to enroll in a monthly program at his local hospital for diet and exercise counseling and other healthcare education. In addition, he was started on lipid-lowering therapy with atorvastatin hydrochloride (20 mg/d).

The results of Sam's treatment at 12-month follow-up are shown in the *Table*. His hypertension and dyslipidemia were slightly improved. His total cholesterol level was now 154 mg/dL, with an LDL-C level of 96 mg/dL and an HDL-C level of 44 mg/dL. His triglyceride concentration was now 162 mg/dL. Sam's HbA_{1c} level had decreased to 6.9%.

Comment

The management of T2DM and its complications requires a comprehensive, or global, approach that addresses hyperglycemia, hypertension, dyslipidemia, obesity and diet, physical inactivity, and smoking cessation. The initial treatment of the white man who had T2DM in the current case consisted of metformin, an NSAID, a TZD, a thiazide diuretic, an ACE inhibitor; and low-dose aspirin. At 6-month follow-up, the patient continued to have elevated HbA_{1c} levels, hypertension, dyslipidemia, and excess weight. By the 12-month follow-up, additional treatment with metformin combined with the DPP-IV inhibitor sitagliptin, as well as use of a statin and diet and exercise therapy, led to a substantial decrease in HbA_{1c} levels and improved hypertension and dyslipidemia in the patient.

Thus, the patient was successfully treated across the full range of global cardiovascular risk reduction. Nevertheless, there remains a need for new therapeutic approaches with fewer limiting factors for patients with T2DM.

Footnotes

This article was developed in part from a lecture presented at a symposium held September 30, 2007, at a joint American College of Osteopathic Family Physicians/American Osteopathic Association program during the AOA's 112th Annual Convention and Scientific Seminar in San Diego, Calif. Titled “Achieving Glycemic Control in Type 2 Diabetes: The Role of Incretins in Meeting Old Challenges With New Strategies: An Interactive Case-Based Discussion,” this program was supported by an educational grant from Merck & Co, Inc.

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Dr Gavin discloses that he is a consultant to Eli Lilly and Company; LifeScan,

Inc; Merck & Co, Inc; and sanofi-aventis US. He also serves on the speakers bureaus of Eli Lilly and Company and Novo Nordisk US, and he holds stock in Amylin Pharmaceuticals, Inc.

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