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About this Supplement

This supplement was developed in part from presentations 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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Editor's Message

Think Beyond the Numbers, Don't Forget the Patient

Thomas B. Repas, DO

The prevalence of diabetes mellitus in the United States and worldwide is increasing. It is estimated that approximately 20.8 million people in the United States have diabetes mellitus, though the disease remains undiagnosed in 6.2 million of these individuals.¹ Certain ethnic groups are at much higher risk of having type 2 diabetes mellitus (T2DM) than the general population. These groups include African Americans, Hispanic Americans, American Indians, and Asian/Pacific Islanders.¹ In addition, it is estimated that there are 41 million people in the United States with prediabetes.¹ As the US population ages and becomes more obese, the prevalence of T2DM is expected to increase.

Diabetes mellitus is associated with many costly and disabling complications. Excellent glycemic control and management of comorbidities such as hypertension and dyslipidemia have been shown to reduce healthcare costs and improve outcomes.² Nevertheless, many individuals with diabetes mellitus never attain their glycemic goals or other treatment goals. Only 7% of adults with diabetes mellitus achieve the goals of glycosylated hemoglobin (HbA_{1c}) levels of less than 7.0%, blood pressure levels of less than 130/80 mm Hg, and total cholesterol levels of less than 200 mg/dL.²

The reasons that so many patients with diabetes mellitus do not attain treatment goals are complex. Primary care physicians are faced with many hurdles that complicate care of patients with diabetes mellitus: limited time, inadequate reimbursement, lack of support personnel, complexity of treatment, language and cultural barriers, patient nonadherence to treatment plans, a growing underinsured/uninsured population, and a healthcare system better suited for the delivery of acute care than the management of chronic disease.³ Members of minority groups and other underserved populations have a disproportionately high risk of diabetes mellitus and complications. Yet these individuals often receive less than optimal care.^{4,5} Many patients are overwhelmed by the responsibilities of self-management of diabetes mellitus, do not understand the importance of following medical recommendations, or have financial limitations preventing them from taking their medications, testing their blood glucose levels, or returning for follow-up care as advised.

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As our understanding of the pathophysiologic mechanisms of diabetes mellitus increases, so too does the number of pharmacotherapeutic options available to us. Little more than a decade ago, the only medications available to manage T2DM were sulfonylureas, metformin, and insulin. Shortly thereafter, the thiazolidinedione (TZD) class of medications was introduced with troglitazone, which was subsequently pulled from the market because of its association with hepatotoxicity.⁶

Since then, several other antidiabetic agents have been approved by the US Food and Drug Administration, including other TZDs (eg, pioglitazone hydrochloride, rosiglitazone maleate), α -glucosidase inhibitors (eg, acarbose, miglitol), meglitinides (eg, nateglinide, repaglinide), and analog insulins (eg, insulins aspart, detemir, glargine, glulisine, lispro). More recently, new classes of antidiabetic agents have become available, including the incretin mimetics (eg, exenatide), the amylin analogs (eg, pramlintide acetate), and the dipeptidyl peptidase IV (DPP-IV) inhibitors (eg, sitagliptin phosphate).⁷

Although having an arsenal of drugs to choose from has given patients and their physicians a variety of options for T2DM management, it has also complicated care. Understanding the pharmacologic mechanisms of each new category of drugs takes much time and effort. Choosing which medication to add next to a patient's treatment plan can be difficult. To complicate matters further, patients often hear conflicting information about T2DM management from the media and lay press. Many physicians, too, become confused by observations made during postmarketing studies and meta-analyses of medication efficacy and safety in the literature.

In 2007, a meta-analysis by Nissen and Wolski⁸ ignited controversy regarding the potential cardiovascular risk versus benefits of TZDs. Before that study, it was postulated that TZDs might

have antiatherogenic benefits independent of their effects on glycemic control. Research had shown that both pioglitazone and rosiglitazone appeared to produce benefits on inflammatory markers and other markers of atherosclerotic risk, as well as improvements in carotid intima-media thickness (CIMT).⁹⁻¹² Furthermore, the PROactive study¹³ suggested that pioglitazone may be associated with benefits in regard to all-cause mortality, stroke, and myocardial infarction. On the contrary, the meta-analysis by Nissen and Wolski⁸ suggested that there may be increased risk of myocardial infarction associated with rosiglitazone. However, an interim analysis of the RECORD study¹⁴ did not show a statistically significant difference for myocardial infarction risk between the group receiving rosiglitazone and the control group.

Unfortunately for physicians and other healthcare providers, there is no definitive answer regarding how all this research information should affect practice until the results of more rigorous clinical studies become available. As noted in the article by James R. Gavin III, MD, PhD, in this *JAOA* supplement, some physicians and patients have elected to switch to an alternative TZD, while others have chosen to change to another family of antidiabetic agents altogether.

As described in all three of the illustrative cases presentations in this *JAOA* supplement (written by Dr Gavin; Jeffrey S. Freeman, DO; and Craig W. Spellman, DO, PhD), clinicians treating patients with T2DM must address many issues besides glycemic control alone, including hypertension, dyslipidemia, and other comorbidities. In addition, they must screen their patients for the microvascular and macrovascular complications of diabetes mellitus. Microalbuminuria is not only a marker of increased risk for renal insufficiency, but also a marker of endothelial dysfunction and increased risk of cardiovascular events.¹⁵ Patients with diabetes mellitus

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frequently have various other medical problems complicating their treatment. For example, they are at higher risk of depression, obstructive sleep apnea, and nonalcoholic fatty liver disease.^{16,17}

The guidelines for the management of diabetes mellitus continue to become more aggressive. It is difficult for a busy physician to keep up to date on all of the guidelines, but it is even more challenging to actually reach these treatment goals with patients.

The American Diabetes Association (ADA) recommends an HbA_{1c} goal of less than 7.0%.⁷ However, the ADA also suggests that HbA_{1c} levels be as close to normal as possible (<6.0%) in selected patients without causing hypoglycemia—per the discretion of the clinician.⁷ The American Association of Clinical Endocrinologists recommends an HbA_{1c} level of 6.5%.¹⁸

Recently, however, the intensive treatment arm of the ACCORD study was halted 18 months early after it was noted that overall mortality was increased in patients who were at high risk for cardiovascular disease.¹⁹ The intensively treated patient group (half of whom achieved an HbA_{1c} level of less than 6.4%) had increased overall mortality, compared with the less intensively treated patient group (half of whom achieved an HbA_{1c} level of less than 7.5%). However, both patient groups had a significantly lower mortality than had been reported in other studies. The cause of mortality and other contributing factors were unknown, though there did not appear to be any difference in mortality associated with the various medications that were used, including rosiglitazone.¹⁹

It is too early to understand how such preliminary results should affect clinical practice. Numerous prior studies have suggested that individuals with T2DM who achieve better glycemic con-



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control are at lower risk for complications.⁷ Less stringent glycemic goals may be more appropriate for patients with hypoglycemic unawareness, frail elderly patients, and patients who are at high risk for cardiovascular disease—at least until we have a better understanding of the reasons that overall mortality was increased in the intensively treated group in the ACCORD study.¹⁹ Patients with new-onset diabetes mellitus who do not fall into any of the foregoing categories may still benefit from more aggressive glycemic control with monitoring.

Previously, the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III)^{20,21} suggested a low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL as the goal for patients at the highest cardiovascular risk, with a more aggressive LDL-C goal of less than 70 mg/dL as an option left to the discretion of the clinician. However, the ADA and the American College of Cardiology Foundation²² recently released a joint consensus statement recommending an LDL-C goal of less than 70 mg/dL, a non-high-density lipoprotein cholesterol (non-HDL-C) goal of less than 100 mg/dL, and an apolipoprotein B goal of less than 80 mg/dL for patients with diabetes mellitus and one or more cardiovascular risk factors (eg, smoking, hypertension, and/or

family history of premature coronary artery disease).

Type 2 diabetes mellitus and insulin resistance are associated with mixed dyslipidemia. Although the LDL-C levels may not be all that high in patients with T2DM, other lipid abnormalities, including hypertriglyceridemia, low HDL-C level, elevated apolipoprotein B level, an increased number of small dense LDL-particles (LDL-P), and an increased number of

total LDL-P are often present in these patients.^{23,24} This combination of dyslipidemic factors is thought to be particularly atherogenic,²³ and research suggests that it is often impossible to reach lipid goals in such patients with monotherapy alone.²⁴

Statins are the first-line agents for lowering LDL-C and LDL-P, with strong evidence supporting their cardiovascular benefits. However, many patients do not achieve LDL-C targets and other lipid goals by using statins alone. Some patients are intolerant of statins. For these individuals, additional antihyperlipidemic medications need to be considered, including niacin, fibrate, ezetimibe, bile acid sequestrants, plant sterols or stanols, and omega-3 fatty acids.²⁵

Amid the controversy surrounding the TZDs, the benefits of ezetimibe in combination antihyperlipidemic therapy for lowering LDL-C levels has also been recently questioned. In the ENHANCE study,²⁶ patients with familial hypercholesterolemia who were treated with combined therapy of simvastatin and ezetimibe had significant reductions in LDL-C, triglyceride, and C-reactive protein levels, compared with patients receiving treatment with simvastatin alone. However, despite the positive changes in these parameters, the group receiving combined therapy surprisingly did not have significant improvements in ultrasonographic measurements of their CIMT—a surrogate marker for the pro-

gression of atherosclerosis.²⁶ It should be noted that this was not an outcomes-based study; there was no statistically significant difference observed in cardiovascular events.

The reported results of the ENHANCE study²⁶ have caused some physicians to question the benefits of ezetimibe in preventing the progression of atherosclerosis.²⁷ Statins are believed to have pleiotropic effects, in addition to and independent of their LDL-C lowering effects. It is unknown if these effects will result in different outcomes for statins compared with other LDL-C lowering therapies. Other physicians have pointed out that the patients in the ENHANCE study²⁶ had a longer duration of pretreatment with statins compared with patients in other studies. Furthermore, the baseline CIMT of the ENHANCE study was 0.69 mm, much lower than that in previous studies evaluating CIMT.²⁷ Perhaps the potential for further improvement in CIMT was limited because of these factors.²⁸

How the results of the ENHANCE study²⁶ should impact a clinician's decision-making process in antihyperlipidemic management remains unclear. It is difficult to take the results of a study conducted on patients with hypercholesterolemia caused by a genetic defect in the LDL receptor and extrapolate these results to the much more common polygenic mixed dyslipidemia of insulin resistance and T2DM. Also, because the ENHANCE study²⁶ was not designed to evaluate outcomes such as cardiovascular events, we do not know if the further LDL-C lowering observed in the ezetimibe-simvastatin group offers any additional benefit in lowering the rate of future cardiovascular events—despite there being no significant difference in CIMT.

Until further evidence becomes available, physicians should continue to manage dyslipidemia as per our current guidelines. Statins are, and should remain, first-line agents for LDL-C lowering. However, for patients who fail to reach goals on statins alone, or who are statin-intolerant, other antihyperlipidemic agents, including ezetimibe, remain a reasonable option.

As noted in the case presented by

Dr Spellman in this *JAOA* supplement, other disorders, such as osteoporosis, may be present in patients with T2DM. Patients with metabolic syndrome, obesity, and diabetes mellitus—as well as minority populations—are at high risk to have vitamin-D deficiency, predisposing them to low bone mass and osteoporosis.²⁹⁻³¹ It was formerly thought that although T1DM predisposed individuals to the development of osteoporosis, it was assumed that people with T2DM were not at increased risk. That assumption has been shown to not always be correct.³²

To add to the challenges of managing bone disease in patients who have T2DM, it has recently been observed that TZDs may be associated with bone loss and an increased risk of peripheral fracture in women, though not in men.^{33,34} The underlying cause of this association is unclear, but it is theorized to be due to reduced bone formation. The clinical implications of this observation are unknown at present; results of studies evaluating this association are pending.

I remember clearly the advice given to me years ago by an osteopathic physician mentor when I was a medical student: "Think beyond the numbers; don't forget the patient!" That pearl has served me well.

In the care of patients with diabetes mellitus, we spend a great deal of time focusing on the numbers. We follow blood glucose levels, HbA_{1c} levels, blood pressure readings, lipid profiles, and microalbumin-to-creatinine ratios, and we measure body mass index, weight, waist circumference, ankle brachial pressure index, and other parameters. Getting the numbers to goal has been shown to improve outcomes and reduce health-care costs. Routine screening is cost-effective and can prevent complications and premature mortality. Without having numbers to review, it is difficult for clinicians, myself included, to get a clear idea of how to proceed with treatment.

However, osteopathic physicians also understand that their patients are more than simply the sum of their numbers and lab results. Every patient is unique and requires an individualized approach and treatment plan. Screening for complications, getting to treatment

goals, and managing pharmacotherapy are essential—but so too are diabetes mellitus self-management education and therapeutic lifestyle change.

In this supplement to the *JAOA* Drs Freeman, Gavin, and Spellman describe cases revealing how best to manage complex cases of patients with diabetes mellitus and increased cardiometabolic risk. Their articles were developed from 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.

In both their symposium presentations and in their illustrative case presentations in this publication, Drs Freeman, Gavin, and Spellman have indeed provided us with a look beyond the numbers, reminding us not to forget the patient. My mentor would be pleased.

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