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Type 2 Diabetes and Its Complications: A Focus on the Kidneys

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Improving Screening and Diagnosis of Patients With Type 2 Diabetes Mellitus

Managing Patients With Type 2 Diabetes Mellitus: Tight Control Reduces Complications

Understanding Diabetic Kidney Disease: Current Insights

Clinical Pearls and Questions From the Diabetes Educator's Office

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Type 2 Diabetes and Its Complications: A Focus on the Kidneys

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This educational activity is designed for endocrinologists, primary care physicians, nurses, diabetes educators, and other clinicians who treat patients with type 2 diabetes mellitus.

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EDUCATIONAL NEEDS

The burden of type 2 diabetes mellitus (T2DM), in terms of morbidity, mortality, complications, and economic burden, is high and is predicted to rise even further. According to estimates from the US Centers for Disease Control and Prevention (CDC), between 7% and 8% of the population has T2DM, but this is projected to increase to 30% of the population within the next 30 years. The greatest increases are estimated to occur in African Americans and Hispanics, and in women (regardless of race or ethnicity). In addition, although diabetes screening has long been recommended for individuals beginning at around 50 years of age, this is no longer the case. Given the changing—and already altered—demographics of T2DM, clinicians should be monitoring for the disease in all patients over 30 years of age.

Both microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (cardiovascular diseases) complications are consequences of less-than-optimal control of several important clinical parameters in patients with existing T2DM. Therefore, it is crucial that health care providers focus not only on good control of serum glucose but also on blood pressure and lipids as well.

This supplement is designed to provide needed updates in the identification and treatment of patients with T2DM, in order to reduce complications and the societal/medical burden of this disease.

LEARNING OBJECTIVES

By reading and studying this educational supplement, participants should be able to:

- Describe the potential for increased morbidity and accelerated mortality of suboptimally managed T2DM.
- List the risk factors for T2DM and discuss the recommendations for the screening and diagnosis of this disease.
- Discuss methods for identifying patients who may be at high risk for microvascular complications and explain the particular testing and treatment needs of patients who are at risk for renal impairment or failure.
- Critically review and, as necessary, revise existing strategies for building a multidisciplinary, collaborative approach to enhance communication among colleagues, educate patients, and improve treatment, as well as to locate and use quality assessment tools and guidelines.
- Demonstrate improved expertise in the management of patients with T2DM pharmacologic selection and explain the safety and efficacy profiles of antihyperglycemic agents when they are used in combination and/or with insulin.

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Introduction

According to current estimates, about 8% of the population of the United States has type 2 diabetes mellitus (T2DM),[1] certainly an alarming incidence.[2] Of even greater concern is the prediction of the US Centers for Disease Control and Prevention (CDC) that 30% of the population will have T2DM within the next 30 years.[3] Using data from National Health Interview Surveys from 1984 to 2000, Narayan and colleagues[4] estimated that one in every three children born in 2000 will have diabetes by age 50 years (**Figure**); the prevalence is estimated to be higher in certain ethnic groups, including African Americans, those of Southeast Asian ancestry, Hispanics of both genders, and in women regardless of race or ethnicity.

This also means that we can expect a steep rise in the incidence of associated diabetes complications—in particular, retinopathy, neuropathy, cardiovascular disease (CVD), and especially chronic and end-stage kidney disease—and in costs related to caring for patients with these complications. Within the past 12 years, diabetes-related hospitalizations increased by 65%, and a recent report from the CDC indicates that the annual cost of diabetes-related health care in the United States is estimated now at about $180 billion.[5]

Diabetes-related macrovascular changes—manifested clinically as coronary artery disease, myocardial infarction, or stroke—have long been recognized as a principal cause of death in patients with T2DM. However, it should be recognized that microvascular diabetes-related damage can be devastating. With the predicted substantial increase in the incidence of T2DM, we can expect a corresponding increase in the number of patients with blindness, amputations, and chronic kidney disease. Many of these patients will progress to severe renal impairment; a large number will eventually require long-term maintenance on dialysis and/or renal transplantation. In addition—and also very important to recognize—kidney impairment further increases the risk for CVD and CVD-related mortality.[6]

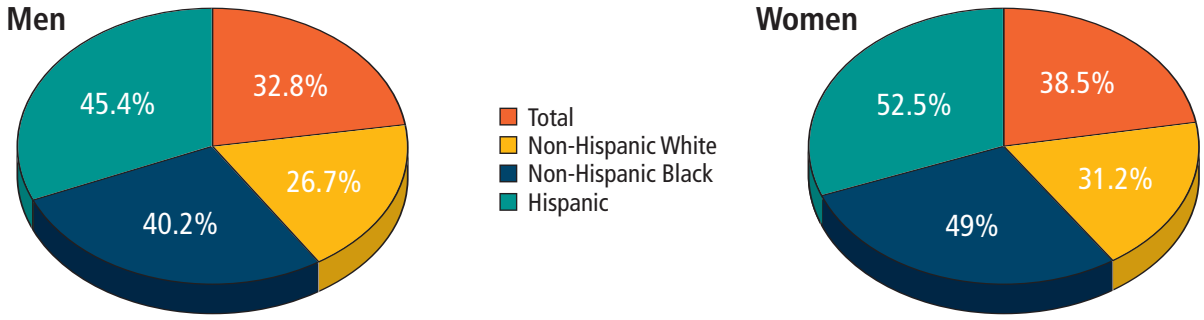
Early intervention involving behavioral and lifestyle changes and appropriate pharmacologic therapy should help us mitigate the dire consequences of morbidity and mortality related to T2DM.

In this supplement, Dr Dace Trence reviews the current recommendations for screening and diagnosis of diabetes. Dr Stuart Shankland discusses the latest information on the pathogenesis and management of diabetic kidney disease. I discuss the implications of recent trials that examine the concept of tight glycemic control of diabetes and its effects on both macrovascular and microvascular complications. I also address the pharmacologic management of T2DM, including the newer classes of drugs, such as glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors, as well as a treatment approach based on the American College of Endocrinology/American Association of Clinical Endocrinologists' algorithm to control the hyperglycemia of diabetes. In the last article, Virginia Valentine, a nurse and diabetes educator, presents observations, insights, and important clinical questions gleaned from recent patient encounters in her practice.

The supplement faculty hopes these perspectives will be of practical value to clinicians who manage patients with T2DM.

Yehuda Handelsman, MD–Chair

Figure. Lifetime Risk for Developing Diabetes Among Individuals Born in 2000



Source: Data derived from Narayan et al.[4] Reprinted with permission.

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Improving Screening and Diagnosis of Patients With Type 2 Diabetes Mellitus

Dace Trence, MD

The recently released statistics and projections from the US Centers for Disease Control and Prevention (CDC) underscore what clinicians have known for decades—that early identification and treatment of individuals with type 2 diabetes mellitus (T2DM) is essential for reducing diabetes-associated morbidity and mortality, particularly those risks related to macrovascular and microvascular complications. Recent discussions in the literature and updated guidelines from professional organizations affect screening and diagnosis and will be discussed here.

Who Should Be Screened? Expanding the Target Population

It has long been recognized that the risk for T2DM rises with increasing age, and, traditionally, the clinical radar screen for T2DM has been set to identify the "typical" at-risk patient: older and overweight. In this group, the incidence of T2DM has remained steady, at approximately one in four in those 60 years of age or older (in 2007, the CDC reported that 12.2 million, or 23.1%, of Americans 60 years of age or older have diabetes).[1] In addition to increasing age and overweight/obesity, traditional risk factors include being in a diabetes-prone ethnic group, having a family history of diabetes, or having a history of polycystic ovary syndrome, gestational diabetes, or metabolic syndrome. However, in recent years, the demographics have begun to shift—not to exclude the previously typical profile, but to expand it to include younger patients and those in at-risk populations.

At-Risk Ethnic/Racial Populations

Recent reports show that the incidence of T2DM in previously recognized high-risk ethnic groups is escalating rapidly. The incidence of diabetes has been increasing—and is projected to continue to increase—in all US populations; however, the greatest increases have been seen in and are projected especially for Hispanics,[2] African Americans,[2] and native Hawaiians and others of Pacific Rim ancestry.[3]

Younger Age Groups

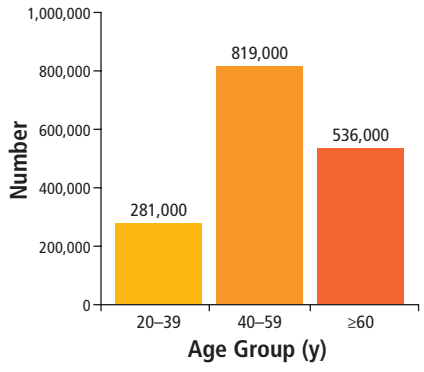
It has become apparent that younger individuals should be screened routinely. The latest statistics from the CDC indicate that the preponderance of new cases of T2DM is projected to occur in populations between 20 and 60 years of age (**Figure**).[4]

It is also important to note that complications of diabetes have a very different picture in patients with T2DM who are less than 40 years of age compared to what is seen in patients 40 years of age or older with T2DM.[5] Complications in the under-40 population tend to be more prevalent as well as more aggressive.[5,6] For example, a 10-fold higher incidence of retinopathy is seen 20 years after diagnosis of T2DM in patients who are less than 40 years of age; a 14-fold higher incidence of myocardial infarction is seen in patients who are less than 40 years of age at the time of diagnosis.[5] These observations underscore the need for detecting T2DM in younger patients.

Patients With Metabolic Syndrome

Increasingly, more attention has been and continues to be given to screening individuals with metabolic syndrome for hypertension and lipid abnormalities because of the association with cardiovascular disease (CVD). It is also important to remember that patients with hypertension, whether requiring antihypertensive treatment or not, also are at increased risk for developing diabetes and should be screened for the disease.[7] In addition, individuals with abnormal lipid profiles—particularly those with elevated triglyceride concentrations—should also be screened for diabetes.[8] Prospective studies have shown a greater than twofold increased incidence in the development of diabetes in individuals with serum triglyceride levels >150 mg/dL.[8]

Figure. Estimated Number of New Cases of Diagnosed Diabetes in People Aged 20 Years or Older, by Age Group, United States, 2007



Source: Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2007. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed December 15, 2010.[4] Reprinted with permission.

Familial and Genetic Links

The traditional associations with overeating and a sedentary lifestyle remain, and these behaviors continue (and, in many cases, actually have worsened) despite the best efforts of clinicians and public health education programs. However, lifestyle risk factors are only pieces of the puzzle and by themselves do not form a complete picture; for example, most people who are sedentary and/or overweight do not develop diabetes, so it is clear that some other factors must be operational. Genetics research will likely provide at least some of the missing pieces, although, to date, efforts to use specific genetic factors associated with T2DM as a reliable predictor for the actual development of future diabetes have not been successful.

An individual who has other family members with T2DM is at increased risk for the disease, but many individuals with T2DM have a family history of both type 1 diabetes mellitus (T1DM) and T2DM. Determining why this should be so will be important to understanding the disease process itself. T1DM is thought to be an autoimmune disease, whereas T2DM is not, so it will be interesting to know how and why both types occur in the same family.

Diagnosis: Observations and Recommendations on the A1C Test

Until recently, guidelines that had been in place for more than a decade provided several criteria for a diagnosis of T2DM: a fasting blood sugar >125 mg/dL on two

separate occasions; or a blood glucose level of >200 mg/dL 2 hours after a 75-mg glucose challenge (administered after a fast of ≥8 hours); or a random blood glucose level >200 mg/dL, fasting or nonfasting, in a patient who also has symptoms such as polyuria, polydipsia, and nocturia. The hemoglobin A1C test (also known as the glycated or glycosylated hemoglobin, or HbA1c test), long recognized as a valuable method of monitoring the effectiveness of diabetes management interventions, including pharmacologic therapy, had not been recommended in the past for screening or diagnostic applications because it was previously considered to be not sufficiently sensitive as a diagnostic tool.

However, in their 2009 report,[9] an International Expert Committee suggested that the A1C test could be used diagnostically and recommended that ≥6.5% be used as a threshold, or cutoff, for a diagnosis of diabetes. In its position paper published in January 2010, the American Diabetes Association (ADA) stated its agreement with the International Expert Committee and updated its own guidelines on diagnosis (**Table 1**).[10] Subsequently, the American Association of Clinical Endocrinologists and the American College of Endocrinology published a joint statement supporting the ADA's position but noted several additional recommendations and considerations (**Table 2**).[11]

Table 1. Diagnosis of Diabetes

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*

OR

3. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 grams of anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, criteria 1 to 3 should be confirmed by repeat testing.
A1C=hemoglobin A1C; DCCT=Diabetes Control and Complications Trial; NGSP=National Glycohemoglobin Standardization Program; OGTT=oral glucose tolerance test.
Source: American Diabetes Association.[10]
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Adjustments may be required in these recommendations sooner rather than later, because very recent literature suggests that the A1C cutoff for a diagnosis of diabetes may not accurately reflect glucose status in some populations. For example, for what actually is the same plasma glucose level, African Americans may have a higher A1C than do persons of Pacific Rim ancestry. A hypothetical example: An A1C of 7% would indicate an average glucose level in the previous 3 months of about 150 mg/dL, yet an African American with an A1C of 7% actually may have had average glucose levels more in the range of 130 to 140 mg/dL, and in an individual of Pacific Rim ancestry, an A1C of 7% may reflect much higher average glucose levels. The differences likely are related to the chemistry of glucose attachment to hemoglobin, and, in some populations, the rate may be very different—either faster or slower—than average.[12]

Furthermore, A1C levels may be elevated as a result of factors unrelated to diabetes—for example, stress hyperglycemia due to a situation such as hospitalization for a serious infectious disease. Hypothyroidism, a common endocrine disorder, has also been shown to affect A1C values, independently of glucose levels.[13]

For all of these reasons, clinicians may wish to consider confirming diagnoses based on A1C by using fasting glucose or 2-hour poststimulation glucose testing in patients who are in any of the populations discussed above, until some of these issues have been further explored in clinical studies.

It should also be emphasized that some A1C systems marketed to clinician offices may be suitable for screening purposes, but any A1C test used for clinical diagnosis should be certified by the National Glycohemoglobin Standardized Program and Diabetes Control and Complications Trial criteria. As the ADA position paper states: "Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes."[9]

Conclusion

Epidemiologic research published recently suggests that limiting clinical vigilance for a diabetes diagnosis to the traditional "at-risk" groups poses a risk for missing individuals outside of these populations. It is becoming increasingly clear that the approach of considering diabetes as a diagnostic possibility only when risk factors dictate is no longer adequate. The current data indicate that clinicians should be aware of the potential for T2DM in virtually all adult patients. Screening should be done routinely in adults, regardless of age, (1) who are in known high-risk groups, including high-risk ethnic/racial groups; (2) who present with conditions—such as myocardial infarction or kidney disease—that may be associated with previously undiagnosed diabetes; (3) who present with signs and symptoms of metabolic syndrome; (4) who have hypertension or lipid abnormalities (especially hypertriglyceridemia); and (5) who are overweight and/or have a sedentary lifestyle. ■

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Table 2. AACE/ACE Recommendations for Using A1C to Diagnose Diabetes*

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinologists (ACE) support the use of a confirmed A1C, with the following recommendations:

- A1C should be considered an additional optional diagnostic criterion, not the primary criterion for diagnosis of diabetes.
- AACE/ACE suggest using traditional glucose criteria for diagnosis of diabetes when feasible.
- A1C is *not* recommended for diagnosing:
  - Type 1 diabetes
  - Gestational diabetes.
- A1C may be misleading:
  - In several ethnic populations (for example, African American patients)
  - In the setting of various hemoglobinopathies, iron deficiency, hemolytic anemias, thalassemias, spherocytosis, and severe hepatic and renal disease.
- AACE/ACE endorse the use of only standardized, validated assays for A1C testing.
- AACE/ACE do not endorse A1C criteria for prediabetes or for those patients at risk for diabetes. AACE/ACE do support an A1C of 5.5% to 6.4% as a screening test for prediabetes if it leads to measurement of a fasting glucose level or performance of a glucose tolerance test for diagnosis.

* This AACE/ACE position statement is based on data available as of February 2010 and may be amended as new data become available. **Source:** AACE/ACE.[11]
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Managing Patients With Type 2 Diabetes Mellitus: Tight Control Reduces Complications

Yehuda Handelsman, MD

In the past 3 years, various publications have raised questions regarding the value of tight glycemic control for people with diabetes, in particular, in relationship to macrovascular disease. These publications were based on several studies that recently appeared in the literature proposing that treating only the cardiovascular risks of people with diabetes—such as dyslipidemia and hypertension—are important in reducing the macrovascular complications of diabetes like heart disease and stroke. These reports raised the question whether intensive treatment for hyperglycemia, per se, is of benefit in terms of cardiovascular outcomes. This point of view ignores the already existing studies demonstrating the cardiovascular benefits of tight glycemic control.[1,2] Furthermore, this point of view ignores, unjustifiably, the proven effects of tight glycemic control in reducing microvascular disease such as neuropathy, retinopathy, and nephropathy.[3,4] Several important, large studies have been published over the past several years that were intended to try to shed light on the role of glycemic control in the comorbidities of diabetes. However, in some cases, the interpretation of early and partial data from these studies have tended to confuse the issue. The goal of this article is to review highlights of these studies and provide clarification that will be helpful in clinical practice.

Large Studies of Intensive Versus Standard Glycemic Control

ACCORD

The first of these studies was the Action to Control Cardiovascular Disease in Diabetes (ACCORD) study.[5] This National Institutes of Health prospective trial, involving more than 10,000 US subjects, was designed to compare the effects of intensive treatment for diabetes control to those of standard care in patients with type 2 diabetes mellitus (T2DM) and cardiovascular risks.

In brief, just over 3 years into the study, the trial was stopped prematurely—and, perhaps, rightfully—because of significant excess mortality in the intensive-treatment group compared to that in the standard-care group. This decision was made before the cause of the excess mortality was known. Interestingly, the data that existed at the time the study was stopped actually showed less incidence of CVD in the intensive-treatment group than in the standard care group. The decision to stop the intensive control arm of the trial led to the false interpretation that the purpose of intensive control is equivalent to a goal of a low glycated hemoglobin (A1C) level and, therefore, created the notion that excess mortality was associated with low A1C levels rather than to the process of achieving tighter control of blood glucose, or even to chance.

Subsequent analysis of the ACCORD data showed that, in fact, of the subjects in the intensive-treatment group, those who achieved lowering of A1C levels to 6.5% or below had better outcomes, particularly with respect to CVD, than the subjects in the standard care group. Of particular interest is that the deaths in the intensive-treatment group occurred in those subjects whose A1C remained above 7% and could not be reduced despite intensive therapy. The correct conclusion is that the mortality in the intensive glucose control arm may have been related to the treatment strategy (perhaps by causing hypoglycemia) or to the refractory nature of hyperglycemia in the group of patients who died (perhaps the result of a different underlying disease process). Clearly, a low target level of A1C, by itself, was not the cause of death.

ADVANCE

The similarly large (more than 11,000 subjects) Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study[6] was a multinational trial involving 215 centers in Asia, Australia, Europe, and Canada and was designed to examine intensive control versus standard of care in patients with T2DM. The ADVANCE investigators showed that intensive glucose control resulted in reductions in both microvascular and macrovascular disease, such as kidney disease and CVD, respectively. However, the improvements were primarily the result of a reduction in microvascular disease, namely, proteinuria, which indicates a reduction of progression to kidney disease rather than a reduction in CVD. Hence, as in the ACCORD trial, the cardiovascular (macrovascular) benefits were not immediately evident, demonstrating that longer trials may be necessary.

VADT

A third important prospective trial was undertaken concomitantly with ACCORD and ADVANCE: the Veterans Affairs Diabetes Trial (VADT),[7] which also had as its purpose an assessment of the potential cardiovascular as well as microvascular benefits of intensive glucose control. The VADT was a prospective study involving approximately 1,800 subjects with poorly controlled T2DM despite treatment with oral antidiabetes medication or insulin therapy. All patients had A1C levels of at least 7.5%. The study was designed to assess the difference in treatment goals of at least a 1.5% reduction of A1C between the intensive-treatment and the standard-treatment groups in macrovascular and microvascular outcomes. In VADT, a difference was seen between the initial report of data and the final report, which led to misconceptions of the effect of tight glycemic control and, ultimately, low A1C levels on diabetes comorbidities. Initially, the VADT investigators stated, apparently erroneously, that "intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of

albuminuria." However, the final results of VADT supported intensive glycemic control to reduce vascular comorbidities in people with T2DM with a duration of less than 15 years.

The initially reported results of VADT, taken together with the initial results of the ACCORD and ADVANCE trials, led many clinicians to the wrong conclusion that intensive control of hyperglycemia in individuals with diabetes to achieve lower A1C goals should not be practiced. However, further analysis of the VADT results has shown that intensive glycemic control was especially beneficial among the subjects in the intensive-treatment group who had had diabetes for fewer than 15 years; the subjects in this subgroup had less microvascular disease as well as less CVD. However, the subgroup of patients with a diabetes duration of more than 21 years had some worsening of cardiovascular status, with a higher mortality rate, perhaps resulting from intensive treatment. (An increase in hypoglycemia was also seen in the intensive-control group in the ACCORD trial, but that finding could not be correlated with an increase in mortality.)

UKPDS

The study with the longest duration is the United Kingdom Prospective Diabetes Study (UKPDS), which involved more than 5,000 patients with newly diagnosed T2DM, enrolled in 23 centers in the United Kingdom between 1977 and 1991.[4] Patients were followed for an average of 10 years, with the objectives of determining whether intensive therapy would reduce macrovascular—that is, cardiovascular—and microvascular complications (nephropathy, neuropathy, retinopathy), as well as comparing three types of treatments: sulfonylureas, metformin, and insulin. In addition, subjects who had concomitant hypertension were randomized to receive treatment aimed at either "tight" or standard blood pressure control; the purpose of this arm was to determine the effect of tight control on outcomes and to compare an angiotensin-converting enzyme inhibitor (in this case, captopril) to a β-blocker (atenolol).

In the UKPDS, the patients in the intensive-therapy arm had lower A1C levels (median, 7.0%) than did those who received conventional therapy (median, 7.9%), with an overall decrease of 25% in the rate of microvascular complications. Here again, the benefits of tight glucose control with respect to CVD were not seen immediately but emerged during an extended (10-year) posttrial follow-up period. The reductions in cardiovascular morbidity and mortality were reported by Holman and colleagues[1] in 2008. These findings are consistent with the long-term follow-up results (ie, of at least 10 years) reported in other trials.[8-10]

Implications for Treatment: Conclusions From Large, Prospective Trials

What is the clinician to make of these findings, and how are these discrepancies to be resolved? Good guidance comes from the meta-analysis published by Ray and colleagues in 2009.[9] These investigators analyzed five prospective, randomized trials (ACCORD, ADVANCE, VADT, and UKPDS, discussed above, as well as the prospective pioglitazone clinical trial in macrovascular events [PROactive][11]) and concluded that intensive glucose control reduces cardiovascular events significantly better than standard control, but with an important caveat: **the optimum mechanism, speed, and extent of A1C reduction *might be different in differing populations*.**

The overriding lesson is that the goal of diabetes treatment should be individualized. No patient should be treated based solely on average reported results. Treatment should be tailored to individual patients' circumstances. It seems clear that a large majority of patients will benefit from achieving the current goals of A1C (≤6.5% per the AACE or ≤6.9% per the American Diabetes Association), provided these levels are achieved safely. It is hoped that most patients who achieve the appropriate goals safely will experience less microvascular disease and, over the long term, will also benefit in regard to macrovascular disease. However, other patients may require different goals.

A subset of patients with T2DM—those with early disease, who are relatively young and otherwise healthy—will probably benefit with treatment to bring A1C levels as close to 5% as possible, *provided* this can be achieved safely, without resulting in side effects such as hypoglycemia or obesity.

Two other subsets of patients—those with long-standing disease (more than 15 to 20 years) who also have comorbid conditions such as heart disease, or those with a shortened life expectancy—probably should not be treated as intensively. No specific goals have been recommended for these patients, but reasonable A1C targets range from 7% to 8% or even 8.5%, with blood sugar levels ranging from a minimum of 100 or 120 mg/dL to a maximum of 250 mg/dL.

Current and Upcoming Treatment Options

This approach of intensive treatment for tight control—or at least, tighter control—is quite possible today because of the availability of medications that do not cause significant side effects and complications. For example, in patients without kidney disease, metformin can be used safely to achieve target goals without causing hypoglycemia. Thiazolidinediones (TZDs) are associated with a risk for weight gain and bone fractures, but when used in patients who are relatively young and healthy, at reasonably low dosages, and in a setting of good clinical follow-up, TZDs can be used safely without causing hypoglycemia.

Newer therapeutic agents in current use and in various stages of development and clinical testing include two classes of incretin-based therapies, the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors. Both GLP-1 receptor agonists and DPP-4 inhibitors work by potentiating signaling of receptors of incretin; these gut hormones (including GLP-1 and glucose-dependent insulinotropic peptide [GIP]) have the ability to affect both fasting and postprandial serum glucose levels. Different agents have different efficacy on postprandial versus fasting glucose levels.

Table. Summary of Key Benefits and Risks of Medications

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease. Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects the relative importance of the benefit or risk.

Medications	Metformin (MET)	DPP-IV Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylureas (SU)	Glinide*	Thiazolidinedione (TZD)	Colesevelam	Alpha-Glucosidase Inhibitor (AGI)	Insulin	Pramlintide
Benefits										
Postprandial glucose (PPG) lowering	Mild	Moderate	Moderate to marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to marked	Moderate to marked
Fasting glucose (FPG) lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Risks										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to severe	Neutral
Gastrointestinal symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe		Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in liver failure of predisposition to lactic acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure/edema	Use with caution in CHF	Neutral	Neutral	Neutral	Neutral	Mild to moderate Contraindicated in class 3-4 CHF	Neutral	Neutral	Neutral	Neutral
Weight gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-drug Interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

*The term "glinide" includes both repaglinide and nateglinide. DPP-IV=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; CHF=congestive heart failure.
Source: American Association of Clinical Endocrinologists. Available at: http://www.aace.com/pub/pdf/GlycemicControlAlgorithmPPT.pdf. Accessed November 20, 2010.[12] Reprinted with permission.

In brief, endogenous GLP-1 has a short (2- to 4-minute) circulating half-life because of rapid degradation by the DPP-4 enzyme and clearance by the kidneys. The GLP-1 receptor agonists were developed to resist DDP-4 degradation, thereby allowing a longer duration of GLP-1 circulation and glucoregulation. The DDP-4 inhibitors work by preventing degradation of the native incretins—like GLP-1 and GIP—resulting in potentiation of their action.

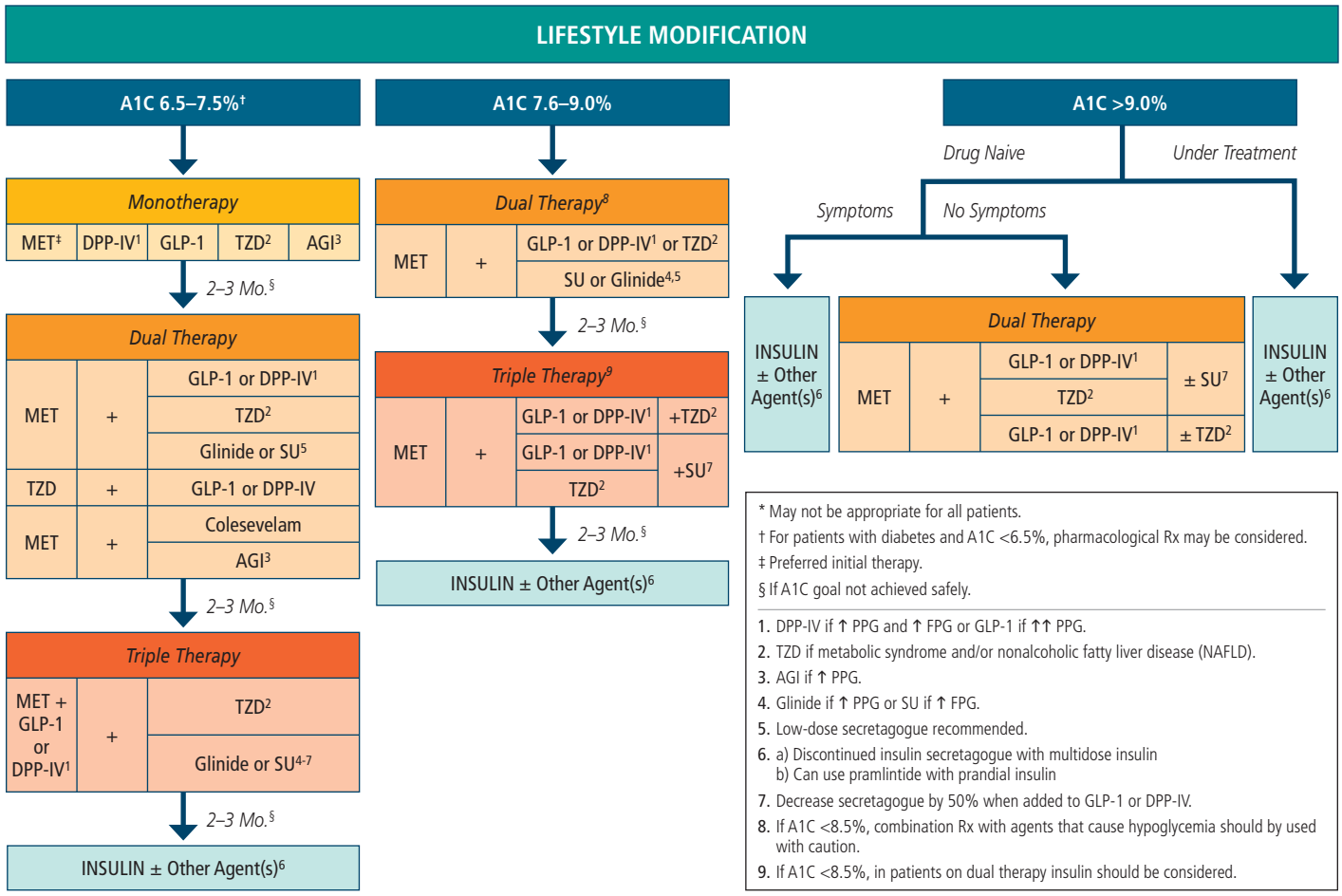
The antihyperglycemic agents, the incretin-based therapies, appear to offer effective glucose control and a lower incidence of hyperglycemia. Some may have effects that result in weight loss and others have a neutral effect on weight.

AACE Treatment Algorithm

As part of their consensus algorithm for the treatment of diabetic hyperglycemia, the AACE developed a table with a summary list of the key benefits and risks of medications (**Table**).[12]

Recognizing that individualized therapy requires a complex program—given the number of medications now

Figure. AACE/ACE Diabetes Algorithm for Glycemic Control (A1C Goal ≤6.5%*)



* May not be appropriate for all patients.
† For patients with diabetes and A1C <6.5%, pharmacological Rx may be considered.
‡ Preferred initial therapy.
§ If A1C goal not achieved safely.

1. DPP-IV if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG.
2. TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD).
3. AGI if ↑ PPG.
4. Glinide if ↑ PPG or SU if ↑ FPG.
5. Low-dose secretagogue recommended.
6. a) Discontinued insulin secretagogue with multidose insulin
   b) Can use pramlintide with prandial insulin
7. Decrease secretagogue by 50% when added to GLP-1 or DPP-IV.
8. If A1C <8.5%, combination Rx with agents that cause hypoglycemia should by used with caution.
9. If A1C <8.5%, in patients on dual therapy insulin should be considered.

AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology; A1C=glycated hemoglobin; MET=metformin; DPP-IV=dipeptidyl peptidase-4; TZD=thiazolidinedione; AGI=alpha-glucosidase inhibitor; SU=sulfonylurea; PPG=postprandial glucose; FPG=fasting plasma glucose; GLP-1=glucagon-like peptide-1.
Source: American Association of Clinical Endocrinologists. Available at: http://www.aace.com/pub/pdf/GlycemicControlAlgorithmPPT.pdf. Accessed November 20, 2010.[12] Reprinted with permission.

available and the need, in many cases, for combination therapy—the AACE convened a panel to develop an expert-based treatment algorithm to help clinicians achieve optimum goals safely (**Figure**).[12] Unlike some previous algorithms, in which the focus was primarily on older medications and on medication costs (and not on safety and the need for individualizing therapy), the AACE algorithm stratifies patients according to A1C levels at baseline and recommends medications based on optimum application and safety, with a special focus on reducing the risk of hypoglycemia, weight gain, kidney disease, and other complications.

Conclusion

The availability of a broad range of medications allows individualization of therapy that is tailored to the patient's needs. The newer medications, which are associated with fewer side effects (including hypoglycemia, weight gain, or kidney disease), allow intensive control to be achieved safely in the majority of patients, reducing the risk for both microvascular and macrovascular complications. Even patients with comorbid conditions, such as CVD and kidney disease, can be treated safely to a reasonable goal of glucose control. ■

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Understanding Diabetic Kidney Disease: Current Insights

Stuart Shankland, MD

Diabetes-related nephropathy (also now called diabetic kidney disease) in patients with type 2 diabetes mellitus (T2DM) is the most common cause of chronic and end-stage kidney disease in the United States, accounting for 44% of new cases of renal failure in 2005.[1] Moreover, the incidence and prevalence is increasing at epidemic proportions countrywide.

Implications of Diabetes-Related Kidney Disease

Unless prevention, early identification, and effective treatment of T2DM result in changes in the course of the disease, clinicians can expect to see a continued steady increase in the number of cases of diabetes and a corresponding increase in cases of diabetes-related microvascular and macrovascular complications. Among the microvascular complications, diabetic kidney disease is perhaps considered the most serious because of its association with life-threatening renal disease (along with the need for dialysis and/or kidney transplantation) and the significant associated risk for cardiovascular disease (CVD).

Diabetic kidney disease should be an important clinical focus for any health care professional who manages patients who have or who are at risk for T2DM. From the standpoint of the kidney itself, diabetic kidney disease is a chronic and progressive condition of end-organ damage and eventual failure. However, proteinuria related to diabetic kidney disease is also an independent risk factor for CVD,[2] and deteriorating renal function is itself an independent risk factor for CVD.[3] The National Kidney Foundation (NFK) reports that 40% to 50% of patients with chronic kidney disease die of CVD, and, in most cases, long before they reach kidney failure.[4]

Natural History of Diabetic Nephropathy

The presentation of diabetic kidney disease has been poorly appreciated because, historically, attention has been paid primarily to increases in serum creatinine levels and/or decreases in estimated glomerular filtration rate (GFR).[5] However, once serum creatinine levels rise and/or estimated GFR decreases, diabetic kidney disease is already well advanced.

Some have proposed that microalbuminuria—defined as <300 mg of protein in 24 hours—should be considered an early sign of diabetic kidney disease. Although any microalbuminuria is an abnormal finding, and this may indeed be a sign of microvascular disease, it does not necessarily indicate the presence of kidney disease. This is particularly true if the serum creatinine and GFR levels are within the normal range. Thus, this finding alone is not diagnostic; similarly, the absence of this finding does not rule out the possibility of diabetic kidney disease in a subset of patients.

The presence of about 300 mg or more of protein in the urine—usually detected by a positive dipstick test—does indicate the presence of kidney disease. Over time, the amount of protein in the urine will increase and the GFR will begin to decrease. These are progressive, and the worsening of the kidney disease depends on a number of factors. Here again, however, a subset of patients may have diabetic kidney disease, but no proteinuria.

Once the serum creatinine levels have increased and/or the estimated GFR has decreased, typically, kidney disease is quite advanced. However, reliance on serum creatinine levels alone in early kidney disease may be misleading. In early kidney disease, the kidneys pass through a phase of hyperfiltration.[6] In this phase, the afferent arteriole dilates and a number of other hemodynamic changes occur within the kidney glomerulus. As a result, the kidney filters more, and, therefore, more creatinine is cleared. Thus, presence of an increased GFR with a seemingly normal serum creatinine level may, in fact, be a very early sign of kidney disease and may reflect this paradoxical phenomenon. For this reason, most nephrologists would recommend using the estimated GFR, and staging patients according to the National Kidney Foundation criteria (**Table**).[4]

Clinicians who treat patients with diabetes are advised by the American Diabetes Association, the American Association of Clinical Endocrinologists, and the NKF to test for microalbuminuria/proteinuria and to monitor estimated GFR annually. As noted, it is important to use both tests, as neither can be considered conclusive when used alone.

Table. National Kidney Foundation Staging Criteria

Stage	Description	GFR, mL/min/1.73 m² (Kidney Function)
1	Kidney damage with normal or ↑ GFR	≥90
2 T	Kidney damage with mild ↓ GFR **for Transplant**	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5 D	Kidney failure **for Dialysis**	<15 (or dialysis)

Among individuals with chronic kidney disease (CKD), the stage is defined based on the level of kidney function using the glomerular filtration rate (GFR), with the higher CKD stages representing lower GFR levels. According to a recommendation from Kidney Disease Improving Global Outcomes (KDIGO), an initiative to improve global outcomes for kidney disease, all kidney transplant recipients should be considered as having CKD based on kidney damage to their native kidney, presumed damage to the kidney transplant, and the need for lifelong care as a result of prior CKD complications and chronic allograft nephropathy. Another recommendation from KDIGO includes an amendment to the CKD classification to use a "T" for all kidney transplant recipients, at any stage, and a "D" for dialysis at stage 5 for people being treated by dialysis.

Source: National Kidney Foundation.[4] Reprinted with permission.

Pathogenesis

The last decade of research has yielded a wealth of information that has enhanced the understanding of the molecular and cellular mechanisms for kidney disease in patients with T2DM.[7] Broadly speaking, research has focused on two main areas. One involves the question of why patients develop proteinuria and, related to that question, what specific strategies may be used to reduce proteinuria at the level of the glomerulus. The second main area concerns the processes of scarring of the glomerulus and the tubular interstitium: Are these processes connected? Or are they independent?

The kidney is such a complicated organ because it has more than 10 different resident cell types, all of which may be responding slightly differently in the diabetic milieu. Some good advances have been made in treatment, but in terms of experimental research, developments have been somewhat hampered by the lack of an ideal animal model that closely replicates and can represent the disease in humans. The animal models used at present fall short of the mark.

Meanwhile, using data from studies with existing—albeit imperfect—animal models as well as the results of cell culture studies, much has been learned about pathologic mechanisms in the kidneys, including tissue production of individual components of the renin-angiotensin-aldosterone system (RAAS),[8,9] advanced glycosylated end products, increased oxidation and oxidative products, and expression of a variety of signaling pathways and growth factors. Thus, a number of candidate pathways have been looked at and even have been successfully blocked in animal models, but, except for the development of some of the RAAS inhibitors, none of these has been effectively translated to the human kidney.

Who Is at Risk for Kidney Disease?

A large body of literature exists exploring two main questions: (1) Can we identify patients with diabetes who will develop kidney disease? and (2) Can diabetic kidney disease be prevented?

Not surprisingly, one general area of great interest in this regard is a possible genetic tendency, which would perhaps be less common in patients with T2DM than in those with type 1 DM. To date, no particular gene or set of genes has been identified that predict reliably that certain patients will or will not develop diabetic kidney disease. Work continues in this arena.

Meanwhile, several so-called soft predictors have been associated with increased risk for diabetic kidney disease. These include poorly controlled diabetes, increasing age and duration of diabetes, the presence of other comorbid conditions such as hypertension, race (eg, diabetic kidney disease is more prevalent in African Americans, Mexican Americans, and Pima Indians), smoking, and a family history of kidney disease.

Among patients who do develop diabetic kidney disease, a number of factors determine how quickly the disease advances. Among these is the presence of certain concomitant conditions; in particular, poorly controlled hypertension, inadequate glucose control, and excess body mass index are associated with more rapid progression of kidney dysfunction. In addition, a family history of diabetes or CVD has also been associated with more rapid progression of kidney disease.

Pharmacologic Intervention

To date, there is no evidence that the onset of diabetic kidney disease can be delayed or prevented in patients who are normotensive. Some small studies involving hypertensive individuals with diabetes have been published demonstrating that the use of inhibitors of RAAS—or RAAS blockers—may retard the onset of kidney disease but not prevent it. These findings raise the question whether all patients with T2DM should receive a RAAS blocker to prevent kidney complications; however, at the moment, no compelling data are available that would support such a strategy.

At this point, no studies have provided convincing evidence that any currently available medications can prevent the onset of kidney disease in patients with diabetes—that is, whether any of these drugs provide some direct benefit to the kidneys at the cellular-molecular level. Studies have demonstrated such benefit in animal models, but as promising as these data may be, robust clinical trials are needed before conclusions can be drawn regarding their benefits in humans. Nevertheless, it is certainly reasonable to infer that effective pharmacologic intervention that leads to adequately controlled blood glucose levels, lipid concentrations, and blood pressure should also improve outcomes in kidney function. (See Dr Handelsman's article on page 7 for a discussion of the data from large studies demonstrating the benefits of these interventions.)

Conclusion

The management of diabetic kidney disease demands diligent screening of patients with diabetes at least once a year, using tests for microalbuminuria/proteinuria and estimated GFR.

In years past, involvement of nephrologists in the care of patients with T2DM was delayed until the point at which a patient's diabetic kidney disease was severe enough to require dialysis. More recently, however, clinical endocrinologists, diabetologists, and nephrologists have begun to work together earlier in an attempt to implement more aggressive strategies designed to delay the otherwise relentless progression to severe kidney damage and end-stage renal disease. Despite the expectation—based on the increase in incidence of T2DM—that an increase would occur in the number of patients requiring dialysis, this has not occurred. Rather than showing an ever-increasing trajectory, the incidence of dialysis actually has flattened in the past few years. A widely accepted inference is that this change in the expected trajectory is the result of these more aggressive interventions—for example, those aimed at reducing the levels of proteinuria—and the earlier expansion of the treatment team to include a specialist in nephrology. ■

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Clinical Pearls and Questions From the Diabetes Educator's Office

Virginia Valentine, CNS, BC-ADM, CDE, FAADE

The team approach to the treatment of type 2 diabetes mellitus (T2DM) is a well-accepted concept, one that physicians, nurses, and diabetes educators agree is important to the successful long-term treatment of patients with diabetes, yet a large number of newly diagnosed patients delay or completely neglect working with the diabetes educator to whom they were referred. According to American Association of Diabetes Educators statistics, less than 30% of individuals with diabetes ever see an educator.[1]

Most endocrinologists work with diabetes educators so their patients have the benefit of diabetes education. However, too many patients are referred for diabetes education after the onset of complications. Commonly, patients are overwhelmed at hearing the diagnosis of diabetes, and it often takes time for them to understand that optimum treatment is a team effort. Follow-up by the clinician's office is crucial to reinforce the importance of the role of the diabetes educator, dietitian, and other members of the treatment team.

Emphasize the Possibilities of Complications—and the Opportunity to Avoid Them

It is not unusual for patients with mild proteinuria or elevated serum creatinine concentration to seem surprised when an educator starts a discussion about managing their kidney problems. The notion of chronic renal disease and the possibility of progression to organ failure likely had been presented in the clinician's office, and most of these patients had not actually heard the message, had not understood it, or had not perceived its importance.

At the time when the diagnosis of diabetes is first discussed, many patients either deny the diagnosis or fail to comply with recommended treatment strategies due to their fear of possible long-term macrovascular and microvascular complications. Just hearing they have diabetes is a lot for patients to absorb, and it is tempting to avoid adding to their distress at that time by not delivering a strong message about potential complications such as blindness and dialysis or kidney transplantation. However, if the "uncomfortable message" comes in two parts, the impact can be overwhelmingly positive rather than just overwhelming.

The second part of the message, of course, is hope—that (1) by achieving glucose, blood pressure, and lipid control goals and by realizing that diabetes is a chronic but manageable disease, the risk for complications can be reduced; (2) if complications do occur, the possible adverse outcomes can be avoided or mitigated with proper treatment; and (3) the diabetes educator's office is the next step, where help is available to learn how to live with diabetes, how to keep the disease under control, and how to implement the strategies that offer the best chances for avoiding complications.

Enhance the Team for Patients With Complications

Traditionally, the diabetes treatment team includes the endocrinologist or diabetologist, the patient's primary care clinician, and a certified diabetes educator. For patients with renal complications, a renal dietitian can be an invaluable addition to the team. These individuals are experts in managing the nuances of nutrition in patients with kidney complications and can determine, for example, when to decrease protein intake in a patient with proteinuria and by how much. In addition to understanding how to manage food, registered dietitians are dietary specialists in this narrow, complex field and are trained to tailor medical nutrition strategies to individual patient needs.

A counselor or psychotherapist can also be helpful with patients who experience depression. Although this is not specifically a diabetes-related complication, depression is a common problem in patients with any chronic disease, and it occurs quite often among people with diabetes. It follows that individuals who are depressed are not likely to be able to engage in self-management behaviors and behavioral changes that are essential to living well with a disease such as diabetes. In addition, patients who experience complications such as retinopathy or kidney disease can benefit from the adjunctive support of a mental health professional.

Counteract the "Fault Fallacy"

Too many patients believe that diabetes is as much a character flaw as a disease and that they have it because of bad things they have done or good things they have failed to do. This is particularly true for those who are overweight and who have internalized society's pervasive message that every adverse event that happens to them is their fault because of their weight. Reassurance—and periodic reinforcement—from a health care provider that diabetes is a multifactorial disease and is not their fault supports and help patients feel empowered to take charge of their disease.

Give Patients Permission to Take Care of Themselves

Even patients in the early stages of diabetes whose blood glucose levels are relatively stable on medication should be encouraged to monitor routinely and to use monitoring as biofeedback for understanding the meaning of their blood glucose levels and how food and medications are affecting those levels. Patients who are skilled, knowledgeable, and motivated can manage their own regimens. Understanding how to use self-management tools to manage their disease also gives them a way to regain a sense of control over their bodies and their lives. With guidance, they can learn how to eat the occasional "forbidden" meal and cover it with a medication adjustment. In this context, glucose monitoring is a tool for dynamic self-management rather than just an indication of the status of disease, and a patient's nutritional choice can be just that—and not "cheating."

Questions About Complicated Cases

A number of challenging patient management questions have come up recently in

my practice. Endocrinology colleagues, Yehuda Handelsman, MD, and Dace Trence, MD, whose articles appear earlier in this supplement, have provided responses and comments.

I have seen patients who never show microalbuminuria, yet their serum creatinine level keeps climbing and their glomerular filtration rate (GFR) keeps decreasing. Clearly, by those two findings, these patients have kidney disease, but there is no proteinuria. Is there too much emphasis on microalbuminuria? By focusing on it, are we missing some people who are on a path to renal failure?

Dr Handelsman: There was a short time when the message about microalbuminuria was somewhat unclear. For this reason, both the American Association of Clinical Endocrinologists and the American Diabetes Association now recommend looking at both microalbuminuria and estimated GFR values in all patients with diabetes.

Dr Trence: Microalbuminuria is a screening tool, not a diagnostic test. Of course, kidney disease manifested through a rising serum creatinine level can develop from many causes other than diabetes, so these other possibilities always must be considered in the differential diagnosis. As Dr Handelsman said, both microalbuminuria and serum creatinine levels should be monitored in patients with diabetes. This is particularly important in patients who are on antihypertensive medications or who are using metformin for glycemic control.

I have a patient who had microalbuminuria and who started treatment with the angiotensin-converting enzyme (ACE) inhibitor lisinopril. Shortly thereafter, the microalbuminuria began to decrease until it was almost normal. Is that all we need to do?

Dr Trence: This is indeed an encouraging response to ACE inhibitor therapy, but in addition to good blood pressure control, glycemic control and lipid control are also important to decrease the progression of renal disease in individuals with diabetes. Further, recent attention has been paid to the role of obesity in accelerating a fall-off in renal function, so a reduced caloric intake, when indicated, would also be helpful.

Dr Handelsman: We often see a reduction of 50% or 70% in microalbuminuria in patients on lisinopril, although a reduction to almost normal, as in this patient, is unusual. It is not certain whether the improvement in microalbuminuria is a direct result of the ACE inhibitor or if it is somehow related to blood pressure control. I would keep a patient like this on the ACE inhibitor, but, as Dr Trence points out, we also want to keep blood pressure, serum glucose, and lipids controlled with diet and exercise, not just pharmacologically.

I have noticed that fibrates and fenofibrate raise serum creatinine levels and lower GFR in some patients with T2DM, and if they stop the fibrate, their serum creatinine levels come back down. Should fibrates be stopped when it affects the serum creatinine levels?

Dr Trence: Although this rise in serum creatinine levels might seem alarming, a recently published report showed that, over time, the patients who remained on the fibrate/fenofibrate actually had better renal function than did those who were taken off the medication.[2]

Dr Handelsman: This is a terrific question. We do not know, at this point, whether fibrate causes kidney damage. The same phenomenon with serum creatinine is seen with ACE inhibitors and angiotensin receptor blockers (ARBs); to some extent, the increase in serum creatinine levels with these drugs actually may be a protective mechanism. With ACE inhibitors and ARBs, we suggest that patients stop taking the medications in either of two situations: if the serum creatinine level increases by more than 20% or if the potassium level goes above 5. In the recent ACCORD (Action to Control Cardiovascular Disease in Diabetes) study,[3] fenofibrate was shown to improve retinopathy, a microvascular condition, so it is reasonable to suppose it may exert the same benefit on renal disease. So although we have no recommendations established for dealing with serum creatinine level increases in patients on a fibrate, I would say the same principles we use for ACE inhibitors and ARBs should apply to fenofibrate as well. ■

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A CME-CERTIFIED SUPPLEMENT TO
Family Practice News®
Internal Medicine News®

Type 2 Diabetes and Its Complications: A Focus on the Kidneys

CME Post-Test Answer Sheet and Evaluation Form

Release Date of Activity: February 2011 • **Expiration Date of Activity for AMA PRA Credit:** February 28, 2013

Estimated Time to Complete This Activity: 2.0 hours

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CME Questions

Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

1. **According to the US Centers for Disease Control and Prevention, an estimated ____% of individuals born in 2000 will have type 2 diabetes mellitus (T2DM) by age 50 years.**
   - **A.** 10
   - **B.** 20
   - **C.** 30
   - **D.** 40

2. **The annual cost of diabetes-related health care in the United States is estimated now at about _____.**
   - **A.** $80 million
   - **B.** $180 million
   - **C.** $80 billion
   - **D.** $180 billion

3. **Which one of the following statements regarding the AIC test is correct?**
   - **A.** The A1C test can be used diagnostically, but only when the tests are certified according to the National Glycohemoglobin Standardized Program and Diabetes Control and Complications Trial criteria.
   - **B.** A point-of-care A1C assay is acceptable, but only when performed by a trained health care provider.
   - **C.** The A1C test can be used diagnostically, with a threshold of ≥7.0% indicating a diagnosis of diabetes.
   - **D.** The A1C test should be used only as a screening tool, and not as a diagnostic tool.

4. **Recent reports show that the incidence of T2DM in previously recognized high-risk ethnic groups is escalating rapidly across the board, but the greatest increases have been seen in Hispanics, African Americans, and individuals of _____ ancestry.**
   - **A.** Asian
   - **B.** Mediterranean
   - **C.** Middle Eastern
   - **D.** Pacific Rim

5. **The _____ study/trial of intensive treatment for diabetes control compared to standard care in patients with T2DM was stopped prematurely because of significant excess mortality in the intensive-treatment group; however, further analysis of the data from that study showed that the deaths actually occurred in the subjects with refractory hyperglycemia.**
   - **A.** Action to Control Cardiovascular Disease in Diabetes (ACCORD)
   - **B.** Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)
   - **C.** United Kingdom Prospective Diabetes Study (UKPDS)
   - **D.** Veterans Affairs Diabetes Trial (VADT)

6. **According to the meta-analysis by Ray and colleagues of the ACCORD, ADVANCE, UKPDS, and VADT trials, intensive glucose control reduces cardiovascular events significantly better than does standard control, but _____.**
   - **A.** microvascular disease such as retinopathy is less significantly affected
   - **B.** only in younger patients
   - **C.** only when A1C levels are kept at ≤6.5%
   - **D.** the optimum mechanism, rate, and extent of A1C reduction might be different in differing populations

7. **The American Association of Clinical Endocrinologists' expert-based treatment algorithm for T2DM is based, in particular, on _____.**
   - **A.** achieving A1C levels at or below 6.5%
   - **B.** cost of medications
   - **C.** safety and individualized therapy
   - **D.** use of the newest medications with novel pathways to achieve glucose control

8. **The National Kidney Foundation reports that 40% to 50% of patients with chronic kidney disease die _____.**
   - **A.** because there is an acute shortage of donor organs for transplantation
   - **B.** before 60 years of age
   - **C.** of cardiovascular disease
   - **D.** of end-stage renal disease

9. **Microalbuminuria (defined as <300 mg of protein in 24 hours) _____.**
   - **A.** is sufficient as a diagnostic indicator of the presence of kidney disease
   - **B.** should be used with estimated glomerular filtration rate to monitor regularly for kidney disease
   - **C.** is of no value in diagnosing kidney disease
   - **D.** is meaningless if serum creatinine is normal

10. **More rapid progression of diabetic kidney disease is associated with _____.**
    - **A.** age at onset of T2DM
    - **B.** gender
    - **C.** poorly controlled hypertension
    - **D.** race/ethnicity

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EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. *Please print.*

Name: _____

Specialty: _____

Degree: ❍ MD ❍ DO ❍ PharmD ❍ RPh ❍ NP ❍ RN ❍ BS ❍ PA ❍ Other: _____

Affiliation: _____

Address: _____

City: _____ **State:** _____ **Zip:** _____

Telephone: _____ **Fax:** _____

E-mail: _____

Signature: _____

CME CREDIT VERIFICATION

I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than 2.0 CME credit(s) will be issued for this activity.

COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

- Physicians need up-to-date information on the best therapeutic options to prevent and treat the complications of diabetes, especially renal impairment, which disproportionately affects undertreated patients including the elderly and those in high-risk ethnic groups.
- Physicians should diagnose renal impairment at early stages before permanent damage has occurred.
- Optimal outcomes for patients with diabetes will be realized only through a multidisciplinary, system-wide, cooperative approach that emphasizes patient education and practice recommendations.
- Physicians need updated information on existing and emerging medications for type 2 diabetes for patients who have renal impairment or are at risk for developing it.

Did participating in this educational activity improve your KNOWLEDGE in the professional practice gaps that are listed above?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer. _____

_____

_____

Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed above?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer. _____

_____

_____

Did participating in this educational activity improve your PERFORMANCE in the professional practice gaps that are listed on the left?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer. _____

_____

_____

Please identify a change that you will implement into practice as a result of participating in this educational activity (new protocols, different medications, etc.) _____

_____

_____

How certain are you that you will implement this change?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

What topics do you want to hear more about, and what issue(s) in your practice will they address? _____

_____

_____

Were the patient recommendations based on acceptable practices in medicine? ❍ Yes ❍ No

If no, please explain which recommendation(s) were not based on acceptable practices in medicine. _____

_____

_____

Do you think the articles were without commercial bias? ❍ Yes ❍ No

If no, please list the article(s) that were biased. _____

_____

_____

The University of Louisville thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients' care.

CME INSTRUCTIONS

This educational supplement provides 2.0 free *AMA PRA Category 1 Credits*™. Access to http://platform.rievent.com/globalacademy/FPIM and print your certificate online.