BEST PRACTICES IN: Renal Impairment in Patients With Type 2 Diabetes: an Important Determinant of Treatment Selection

Introduction

Diabetes mellitus (DM) represents a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] Type 2 DM (T2DM), which is said to account for 90% to 95% of all cases of diagnosed DM, is characterized by insulin resistance and a relative insulin deficiency.[1] Approximately 24 million Americans have type 1 or type 2 DM (diagnosed and undiagnosed), and this number is expected to increase to 44 million by 2034.[2] It is estimated that 57 million Americans had prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in 2007.[3]

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Complications Associated With T2DM

Much of the patient and societal burden associated with T2DM results from the long-term complications of the disease. Patients with T2DM are at an increased risk for macrovascular and microvascular complications. Macrovascular complications include coronary heart disease (CHD), stroke, hypertension (HTN), and peripheral vascular disease (PVD), and microvascular complications include nephropathy, retinopathy, and neuropathy.

Macrovascular Disease: About 75% of patients with T2DM also have HTN,[4] which increases the risk for other macrovascular diseases associated with T2DM.[5] CHD is common in patients with T2DM with heart disease noted on 68% of DM-related death certificates among people aged ≥65 years.[4] Patients with T2DM have a 2- to 4-fold higher risk of death from CHD than nondiabetics.[4] PVD is a significant independent risk factor for lower-limb amputation in this population.[6] Patients with T2DM have a 2- to 4-fold higher risk for stroke than nondiabetics, and stroke is noted on 16% of DM-related death certificates among people aged ≥65 years.[4]

Microvascular Disease: Microvascular disease also occurs frequently in patients with T2DM. Diabetic retinopathy results in 12,000 to 24,000 new cases of blindness each year in the United States, and DM is the leading cause of new cases of blindness in adults aged 24 to 70 years.[4] Neuropathy due to DM has been reported to occur in 60% to 70% of patients with this disease; this includes peripheral neuropathy, gastroparesis, and erectile dysfunction.[4] Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months[7] and has been estimated to affect 50 million people worldwide and 11% of the US population.[8] Approximately 40% of adults diagnosed with DM also have CKD.[9] Approximately 44% of all CKD in the United States is due to DM.[4]

Epidemiology of CKD/RI With DM

CKD and renal impairment (RI) occur in a high percentage of adults with DM or prediabetes in the United States. Using data from the Fourth National Health Education and Nutrition Survey (NHANES IV), a cross-sectional analysis of patients with T2DM indicated that 40% of patients with DM also had CKD.[10] Given an adult DM population of 24 million, this equates to nearly 10 million individuals.[4,10] Approximately 17.7% of people with prediabetes have CKD.[9] With an estimated prediabetes population of 57 million, this equates to >10 million people.[4,9] Thus, ~20 million people who have, or are at risk for, DM have evidence of CKD. The National Kidney Foundation has defined five stages of CKD based on GFR (Table 1).[7]

Risk Factors for CKD/RI in Patients With DM

Risk factors for susceptibility to, and initiation of, CKD (not necessarily associated with T2DM) can be categorized into two groups: clinical factors and sociodemographic factors. Clinical factors include DM, HTN, autoimmune disease, systemic infections, urinary tract infections, urinary stones, lower–urinary tract obstruction, neoplasia, family history of CKD, and recovery from acute renal failure. Sociodemographic factors include older age, African American or American Indian race, exposure to certain chemical and environmental conditions, and low income/education levels.[7]

Epidemiologic studies have demonstrated significant associations between several patient-related factors and increased risk for the development of CKD in patients with T2DM. Results from a study in adults with T2DM indicated that elevated levels of urinary albumin, total cholesterol, glycated hemoglobin (HbA_{1c}), male sex, and the presence of retinopathy were risk factors for incipient or overt diabetic nephropathy,[11] while another study demonstrated that elevated mean blood pressure, plasma cholesterol levels, and hyperglycemia were the main risk factors associated with the development of diabetic nephropathy.[12]

The frequencies of microalbuminuria (urinary albumin excretion 30 to 299 mg/24 hr) and macroalbuminuria (urinary albumin excretion ≥300 mg/24 hr) are increased in patients with DM.[7] Observational studies of patients with T2DM have also shown that higher baseline urinary albumin excretion (14 vs 7 mg/24 hr) was associated with an increased risk for the development of CKD.[11] Results from the Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study showed a linear relationship between baseline albuminuria in patients with T2DM and risk for kidney disease.[13] That is, for all baseline risk markers (age, gender, cholesterol, serum creatinine, albuminuria, hemoglobin, and HbA_{1c}), albuminuria was the strongest predictor of kidney disease. Patients with high baseline albuminuria (≥3.0 g/g creatinine) showed a 5.2-fold increase in renal end point (doubling of serum creatinine, end-stage renal disease [ESRD], or death) and an 8.1-fold increase in risk for progressing to ESRD compared with the low albuminuria group (≤1.5 g/g creatinine).[13]

Early Identification and Screening

Timely intervention can decrease the risk for, and slow the progression of, nephropathy in patients with T2DM. Thus, it is important that renal function be assessed in affected patients. The American Diabetes Association (ADA) recommends an annual evaluation of urinary albumin excretion in patients with T2DM and at least an annual assessment of serum creatinine/estimated GFR (eGFR).[14] Screening for microalbuminuria can be performed by measuring the albumin/creatinine ratio (ACR) in a random spot urine test. Timed or 24-hour urine collections are bothersome and do not add to the accuracy of this test.[14] Persistent microalbuminuria (30 to 299 mg/24 hr) is an early clinical marker for the development of nephropathy in patients with DM.[14] Serum creatinine values should be used to estimate GFR by the Modification of Diet in Renal Disease (MDRD) equation or the Cockcroft-Gault formula, although recent results have indicated that the MDRD equation may be more accurate.[14] Modifications of the MDRD equation have been shown to improve its accuracy for eGFR in patients with DM and renal dysfunction. Assessment of renal function using eGFR, regardless of the equation or formula used, is much more effective than measuring serum creatinine concentration.[15,16]

Table 1. Stages of CKD and Actions That Should Be Taken for Each Stage

Stage	Description	GFR, mL/min/1.73 m^2	Action
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment, treatment of comorbid conditions, slow progression, reduce risk of cardiovascular disease
2	Kidney damage with mildly decreased GFR	60–89	Estimate progression
3	Moderately decreased GFR	30–59	Evaluate and treat complications
4	Severely decreased GFR	15–29	Make preparations for kidney replacement therapy
5	Kidney failure	<15 (or undergoing dialysis)	Kidney replacement if uremia is present

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
Source: National Kidney Foundation.[7]

Healthcare Providers Are Unaware of the Negative Effects of CKD on Cardiovascular Outcomes in Patients With T2DM

Microalbuminuria and CKD, as reflected by reduced GFR, are significant independent risk factors for the development of cardiovascular (CV) disease in patients with T2DM. Results from the Action in Diabetes and Vascular disease: preterAx and diamicroN-modified release Controlled Evaluation (ADVANCE) trial, which involved a large (N=10,640) cohort of patients with T2DM, showed that a urinary ACR >300 mg/g and an eGFR <60 mL/min/1.73 m^2 were independent risk factors for CV events.[17] In fact, these patients had a 3.2-fold higher risk for CV events compared with patients who had neither of these risk factors.[17] These relationships have also been confirmed in earlier studies of patients with T2DM.[18-20] The presence of CKD

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in patients with or without DM has also been associated with increased risk for acute myocardial infarction, cerebrovascular accidents and stroke, PVD, atherosclerotic vascular disease, and congestive heart failure.[21,22] The risk for CV events, including death, in both groups increased progressively with rising albuminuria and declining GFR.[23]

Awareness of CKD/RI: Clinicians

There is a significant lack of awareness by many clinicians of the incidence and effects of CKD in patients with T2DM.[24] This lack of awareness may be responsible for the undertreatment of CKD in this population. Reliance on serum creatinine concentrations for the assessment of renal function may lead to CKD/RI being missed in a substantial proportion of patients. A cross-sectional study of 660 subjects aged 65 to 92 years with normal serum creatinine concentrations (0.8 to 1.3 mg/dL in men and 0.6 to 1.0 mg/dL in women) indicated that 39% had a GFR <60 mL/min/1.73 m^2 according to the Cockcroft-Gault formula and 25% had this degree of renal impairment according to creatinine clearance determined from a 24-hour urine collection.[24] Thus, a substantial proportion of elderly patients have markedly diminished GFR despite normal serum creatinine levels[24] and may not be diagnosed by a routine evaluation of clinical laboratory values.

Awareness of CKD/RI: Patients

Patients with T2DM are generally not aware of CKD/RI when it is present. Results from the NHANES III survey indicated that only 9.2% of subjects with stage 3 CKD were aware of their renal insufficiency.[25] This awareness was increased to only 19.1% of patients with DM and stage 3 CKD.[25] These results are consistent with those from a survey that included 10,266 subjects with CKD (2508 with DM) and showed that 14.4% of subjects with a GFR of 10 to 60 mL/min/1.73 m^2 had a diagnosis of CKD. This value was 15.2% for men and 1.9% for women with DM.[26]

Awareness of CKD/RI: Glycemic Control

The presence of CKD in a patient with DM may significantly increase the risk for hypoglycemia.[27] Results from a retrospective cohort analysis indicated that the frequency of hypoglycemia (plasma glucose concentrations <70 mg/dL) in patients with DM and CKD (eGFR <60 mL/min/1.73 m^2) was twice that in patients with DM but without CKD (10.72 vs 5.33 per 100 patient-months).[28] The increased risk for hypoglycemia in patients with T2DM and CKD/RI is believed to result from lower insulin requirements due to altered metabolism and an accumulation of antidiabetic drugs excreted by the kidney.[29,30]

Prevention and Management

Several studies have demonstrated that controlling four modifiable risk factors—hyperglycemia, HTN, dyslipidemia, and albuminuria—in patients with DM may reduce the risk for, or slow the progression of, CKD. Results from the ADVANCE study showed that intensive glucose lowering to achieve $HbA_{1c} \leq 6.5\%$, as compared with standard therapy, significantly decreased the incidence of new or worsening nephropathy by 21% over 5 years of follow-up ($P=0.006$).[31] Results from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial showed that decreasing blood pressure in patients with T2DM and HTN stabilized renal function over a 5-year period in patients without overt albuminuria at baseline.[32] Results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that lowering cholesterol in patients with T2DM using fenofibrate slowed the progression of albuminuria over 5 years of follow-up.[33] Treatment of patients with T2DM and albuminuria with selective angiotensin receptor blockers (ARBs) or angiotensin–converting enzyme inhibitors (ACEIs) can delay the progression of microalbuminuria to macroalbuminuria and can slow the decline in GFR.[14] Some ACEIs and ARBs are approved for slowing the development and prevention of proteinuria and renal deterioration in patients with T2DM, but others are not.[34]

Results from the Steno-2 trial showed that intensified multifactorial intervention aimed at decreasing hyperglycemia, HTN, dyslipidemia, and microalbuminuria was significantly superior to conventional treatment for decreasing the urinary albumin excretion rate and decreasing the risk for nephropathy.[35] Finally, individuals found to have other modifiable risk factors should be advised to follow a risk factor reduction program.[7]

Conclusion

Studies reviewed in this paper indicate that the number of people with T2DM in the United States is expected to double over the next several decades. As a result, the incidence of complications associated with T2DM (eg, CHD, CKD/RI) are expected to increase as well. Approximately 40% of patients with T2DM develop CKD/RI. Risk factors for CKD/RI in patients with T2DM include inadequate glycemic control, albuminuria, HTN, and hyperlipidemia. CKD/RI in patients with T2DM increases morbidity and mortality due to CV events. Results from the ADVANCE study indicated that low eGFR was associated with a 3.2-fold increase in the risk for CV events in patients with T2DM. Thus, physicians and patients need to be more aware of CKD/RI. Early screening and identification of patients with or at risk for CKD using ACR in a spot urine sample and eGFR afford the opportunity for treatment to prevent or delay the progression of CKD/RI. Finally, the presence of comorbidities and complications makes therapeutic decision-making about glucose-lowering treatment difficult in patients with T2DM.

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