

BEST PRACTICES IN: Type 2 Diabetes Mellitus and Chronic Kidney Disease: Double Trouble?

Introduction

Type 2 diabetes mellitus (T2DM) and its complications account for a considerable and growing disease burden in the United States. The overall prevalence of diabetes mellitus (DM), types 1 and 2, is ~8%, but this increases with age so that its prevalence is nearly 11% in persons aged 40 to 59 years and almost 24% in persons aged ≥60 years.¹ This equates to ~24 million Americans, 17.9 million of whom have been diagnosed with DM and 5.7 million of whom have not. Among Americans with diagnosed DM, 90% to 95% have T2DM.¹

Complications of DM include cardiovascular (CV) disease and microvascular disease (eg, retinopathy, nephropathy, neuropathy). CV disease is the leading cause of mortality in patients with DM, with heart disease noted on 68% of DM-related death certificates among people aged ≥65 years.² Adults with DM have death rates from heart disease that are 2 to 4 times greater than those in people without DM.² Diabetic kidney disease (DKD) is also emerging as a major cause of morbidity and mortality. The incidence of DKD is increasing in the United States, with the growth in DM prevalence and the aging of the population. In 2005, DM was reported to account for 44% of new cases of renal failure, and DKD is now the leading cause of kidney failure in the United States.² Over the past 2 decades the incidence of end-stage renal disease (ESRD) due to DM has doubled in the United States while the prevalence of chronic kidney disease (CKD) among the general Medicare population with DM and hypertension increased 4-fold.³ DKD has traditionally been defined in terms of elevated urinary albumin excretion, either as microalbuminuria or macroalbuminuria. In a large, global, cross-sectional study of 32,000 patients with T2DM in 33 countries, the prevalence of microalbuminuria and macroalbuminuria was ~39% and 10%, respectively.⁴ The development of albuminuria is associated with a decline in kidney function. Over a median of 15 years, 38% of the 4031 patients with T2DM in the UK Prospective Diabetes Study (UKPDS) developed albuminuria and 29% of 5032 subjects developed renal impairment, defined as creatinine clearance <60 mL/min or a doubling of their plasma creatinine concentration.⁵

A CKD staging classification has been developed by the National Kidney Foundation (NKF) and is based on esti-

mated glomerular filtration rate (eGFR) using serum creatinine measurement and the Modification of Diet in Renal Disease (MDRD) equation (Table 1).^{3,6} A study of 1197 patients with T2DM from the Third National Health and Nutrition Examination Survey (NHANES III) found that 13% had an eGFR <60 mL/min/1.73 m² or stage 3 CKD. Approximately 40% of these individuals did not have increased urinary albumin excretion (defined as a spot urine albumin/creatinine ratio [ACR] ≥17 mg/g in men and ≥25 mg/g in women).³ In the more recent NHANES 1999–2006 survey of 1125 participants with

diagnosed and undiagnosed DM, the prevalence of CKD stages 1 through 4, defined as eGFR 15 to 59 mL/min or ACR ≥30 mg/g, was 39.6% in individuals with self-reported, provider-diagnosed DM and 41.7% in individuals with previously undiagnosed DM.⁷ Among patients with CKD, the prevalence of stage 3 and 4 disease was 39.0% and 40.6% for diagnosed and undiagnosed DM, respectively.⁷ Albuminuria was not present in 81% and 79% of these individuals, respectively.⁷ These data emphasize the importance of serum creatinine measurement

and eGFR during screening, in addition to urine tests for albumin to identify DKD.

Early Identification and Screening

The American Diabetes Association (ADA) Standards of Medical Care recommend annual testing to assess urine albumin excretion in all patients with T2DM starting at diagnosis.⁸ Screening for microalbuminuria is most conveniently done by measuring the ACR in a random spot urine sample. Twenty-four-hour or timed collections are more burdensome and add little to prediction or accuracy, and the measurement of urinary albumin by dipstick or other methods without simultaneous urine creatinine measurement is less accurate.⁸ Microalbuminuria is diagnosed when the spot collection shows 30 to 299 μg albumin/mg creatinine, and macroalbuminuria is diagnosed when the spot collection shows ≥300 μg albumin/mg creatinine; these results should be documented in 2 to 3 specimens collected within a 3- to 6-month period.⁸ Persistent microalbuminuria (30 to 299 mg/24 hr) is an early clinical marker for the development of nephropathy in patients with DM.⁸

In addition to the identification of abnormal urinary albumin excretion, the ADA recommends at least annual measurement of serum creatinine and eGFR by laboratories using the MDRD equation and staging of CKD according to the NKF classification.⁸ Serum creatinine levels by themselves are not an adequate measure of kidney function.⁶ The MDRD method of estimating GFR is recommended because it has been suggested to be more accurate than the Cockcroft-Gault formula.⁸ GFR calculators are available at http://www.nkdep.nih.gov/professionals/gfr_calculators/⁸

DKD Increases the Risk of Renal Failure and CV Disease

The consequences of kidney disease in people with T2DM include progression to renal failure requiring dialysis or

transplantation, and an increased risk of death. In the UKPDS, the rate of progression from normoalbuminuria through microalbuminuria, macroalbuminuria, and elevated plasma creatinine concentrations or the need for renal replacement therapy was 2% to 3% per year.⁹ Annual death rates increased with worsening nephropathy, and patients with elevated plasma creatinine concentrations or renal replacement therapy had an annual death rate of 19.2%, including 4.0% who died of uremia.⁹ In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study evaluating various risk factors for the development of renal disease in patients with T2DM (age, gender, cholesterol, serum creatinine, albuminuria, hemoglobin, and glycated hemoglobin [HbA_{1c}]), albuminuria was the strongest predictor for the development 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, 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).¹⁰

In addition to accelerated renal failure and death, diabetic nephropathy and CKD have been established as independent risk factors for the development of CV disease. Microalbuminuria was shown to be an independent risk factor (relative risk [RR], 1.83; 95% confidence interval [CI], 1.64 to 2.05) for major CV events in 9043 high-risk patients with CV disease or DM followed for 5 years. CV events were increased by 6% for every 0.4–mg/mmol increase in ACR.¹¹ In a T2DM cohort of 840 patients, microalbuminuria and gross proteinuria increased the risk for CV mortality over 12 years, independent of other factors, including age, gender, glycemic control, insulin use, CV disease history, retinopathy severity, and antihypertensive therapy use (adjusted RR, 1.84; 95% CI, 1.42 to 2.40 and RR, 2.61; 95% CI, 1.99 to 3.43, respectively).¹² CKD, identified by reduced eGFR (<60 mL/min/1.73 m²) by the MDRD equation, had an independent graded association with the risk of CV events and all-cause mortality in a study of 1.1 million adults with and without DM in the Kaiser Permanente healthcare system.¹³ In 10,640 patients with DM from the Action in Diabetes and Vascular disease: preterAx and diamicroN–modified release Controlled Evaluation (ADVANCE) trial, a halving of baseline eGFR was associated with a 2.2-fold increase in the multivariable adjusted risk of CV events and a 3.6-fold increase in the risk of CV death. A 10-fold increase in urinary ACR was associated with 2.5- and 3.9-fold increases in the risks of CV events and CV death, respectively.¹⁴ Patients with urinary ACR >300 mg/g and eGFR <60 mL/min/1.73 m² had a 3.2-fold higher risk for CV events and a 5.9-fold higher risk for CV death (Figure 1).¹⁴

The combination of DM and kidney disease thus amplifies the risk for CV disease associated with each disease separately, in addition to hastening the onset of renal failure. In the UKPDS, CV disease was the most common cause of death at all stages of CKD, with an increasing risk for CV death with increasing nephropathy (*P*<0.0001).⁹

Interestingly, the impact of renal disease on mortality in patients with type 1 DM (T1DM) was recently studied. Over a median follow-up of 20 years, individuals with childhood-onset T1DM with no evidence of microalbuminuria (albumin excretion of 20 to 200 μg/min), overt nephropathy (albumin excretion of >200 μg/min), or ESRD (the need for dialysis or renal transplantation) had survival rates similar to those of the general population. Individuals with renal disease had mortality that was 6.2-fold higher than expected, with standardized mortality ratios of 2.0 for patients with normoalbuminuria, 6.4 for patients with microalbuminuria, 12.5 for patients with overt nephropathy, and 29.8 for patients with ESRD.¹⁵



John Gerich, MD
Emeritus Professor of Medicine
University of Rochester
Rochester, NY



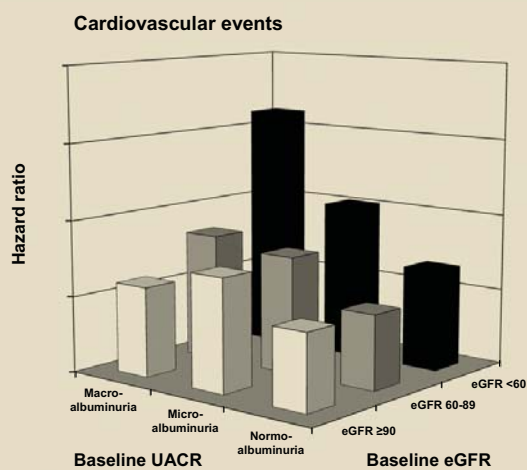
Michael Kodack, PharmD
Vice President,
Medical
BlueSpark Healthcare
Communications LLC
Basking Ridge, NJ

Table 1. Stages of CKD

Stage	Description	GFR, mL/min/1.73 m ²
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 (or undergoing dialysis)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
Source: Levey et al⁶

Figure 1. Combined Effects of Albuminuria and eGFR Levels for Risk of CV Events



Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Source: Reproduced with permission from Ninomiya et al.¹⁴

Preventing Nephropathy

Evidence-based strategies can prevent the progression of nephropathy in patients with T2DM. The use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has been shown to prevent nephropathy progression and is recommended in the ADA Standards of Medical Care for nonpregnant patients with DM and microalbuminuria or macroalbuminuria.⁸ Large prospective trials have demonstrated that ACEIs and ARBs can reduce the development of nephropathy and the incidence of major CV disease outcomes in people with T2DM.¹⁶⁻¹⁸ Some ACEIs and ARBs are approved for slowing the development or prevention of proteinuria and renal deterioration while others are not. Optimizing glucose control is recommended by the ADA Standards of Medical Care to reduce the risk or slow the progression of nephropathy.⁸ Based on the results of recent large, prospective trials of intensive glycemic control in people with T2DM, the ADA guidelines recommend lowering HbA_{1c} to <math>< 7\%</math> to reduce microvascular complications.⁸ In the 10-year follow-up of intensive glucose control in the UKPDS study, microvascular disease was reduced significantly, by 24% ($P=0.001$).¹⁹ In the ADVANCE study, patients in the intensive glycemic control group, with a mean HbA_{1c} of 6.5%, experienced a significant reduction in major microvascular disease, with a significant 21% reduction in new or worsening nephropathy ($P = 0.006$).²⁰ In a follow-up to the Steno-2 study, 160 patients with T2DM and persistent microalbuminuria who had been randomized to receive intensive or conventional therapy for a mean of 7.8 years were followed observationally for an additional 5.5 years.²¹ Intensive therapy (consisting of lower thresholds for blood pressure [BP], HbA_{1c}, cholesterol, and the use of ACEIs and aspirin therapy) was shown to slow the progression of, and reduce the risk for, the development of nephropathy compared with conventional therapy at 4 and 8 years, and was maintained during an additional 5.5 years of post-trial observation.²¹ During the observation period, 20 patients in the intensive-therapy group (compared with 37 patients in the conventional-therapy group) developed diabetic nephropathy (RR, 0.44; $P=0.004$).²¹ Finally, in the Veterans Affairs Diabetes Trial (VADT), intensive glycemic control significantly reduced any increase in albuminuria by nearly 34% ($P=0.01$).²² Therefore, for selected individuals, such as those with recent-onset DM and no significant CV disease, providers might suggest HbA_{1c} goals lower than <math>< 7\%</math> if they can be achieved without significant hypoglycemia or other adverse effects.⁸

The ADA guidelines recommend optimizing BP control to reduce the risk or slow the progression of nephropathy.⁸ The current ADA BP target is <math>< 130/80</math> mmHg;

based on patient characteristics and response to therapy, higher or lower BP targets may be appropriate.⁸

In view of the increased CV risk and prevalence of dyslipidemia associated with DM and CKD, statin treatment is recommended for people with these disorders.²³ The current ADA low-density lipoprotein (LDL) cholesterol target is <math>< 100</math> mg/dL; in individuals with overt CVD, a lower LDL cholesterol goal of <math>< 70</math> mg/dL, using a high dose of a statin, is an option.⁸ The effects of cholesterol lowering with statins for reducing major CV events in people with DM are well established and extend to people with CKD who are not yet undergoing dialysis. Trials of people undergoing dialysis have not shown significant benefits.^{23,24} Statins may also slow the progression of nephropathy and decline in GFR, although data are limited.²⁴

Pharmacologic Considerations for Patients With DKD

The treatment of patients with T2DM should be directed at lowering HbA_{1c} to below or around 7% to reduce microvascular and neuropathic complications.⁸ With regard to macrovascular risk reduction, a general HbA_{1c} goal of <math>< 7\%</math> seems reasonable for many adults. A less-stringent HbA_{1c} goal may be appropriate for some patients (eg, those with a history of severe hypoglycemia, those with advanced macrovascular complications).⁸ In patients with CKD starting at stage 3 (GFR <math>< 60</math> mL/min/1.73 m²), the risk of hypoglycemia is increased because reduced kidney function affects the clearance of endogenous insulin; decreases renal gluconeogenesis, thus reducing its contribution to blood glucose; and slows the renal excretion of some glucose-lowering drugs.²³ The kidney is responsible for metabolizing one third of circulating insulin so patients with T2DM must pay extra attention to their blood glucose levels and, in conjunction with their healthcare provider, reduce their doses of hypoglycemic medications, as indicated, to avoid hypoglycemia.

Awareness of CKD in Patients With DM

Although the importance of identifying nephropathy and staging CKD to prevent renal progression and manage elevated CV risk is established and advocated by the ADA and other professional organizations, there is a gap between evidence and practice. Clinical laboratories do not routinely report eGFR, and the level of awareness of CKD is low among providers and patients. In a random sample of >6000 clinical laboratories conducted between 2006 and 2007, only 38.4% of laboratories reporting serum creatinine concentrations also reported eGFR, and, among those, only two thirds reported it routinely.²⁵ When eGFR is reported, physicians do not routinely diagnose CKD. In a review of patients in the Kaiser Permanente healthcare system with reduced eGFR (>10 to <math>< 60</math> mL/min/1.73 m²), only 14% of subjects had CKD documented in the electronic medical record and only 22% had it documented for patients with DM.²⁶ Low patient awareness was also found in an analysis of NHANES 2003–2004 survey participants who had serum creatinine measured; <math>< 10\%</math> of those with

CKD stage 3 and <math>< 50\%</math> of those with CKD stage 4 said that they had been told by a physician that they had weak or failing kidneys.²⁷

Conclusion

Nephropathy and renal insufficiency are common complications of T2DM that may progress to renal failure and are associated with increased CV risk. Physicians should screen their patients with T2DM by determining their ACR annually in a spot urine sample, and serum creatinine testing with eGFR by the MDRD equation and CKD staging according to the NKF classification. Early intervention with evidence-based treatments can prevent or delay the progression to renal failure and can reduce the elevated CV risk in individuals with DKD. The presence of comorbidities and complications can complicate therapeutic decision-making in patients with T2DM.

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