Update on Diabetic Nephropathy: Core Curriculum 2018

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Diabetic kidney disease and diabetic nephropathy are the leading cause of end-stage kidney disease in the United States and most developed countries. Diabetes accounts for 30% to 50% of the incident cases of end-stage kidney disease in the United States. Although this represents a significant public health concern, it is important to note that only 30% to 40% of patients with diabetes develop diabetic nephropathy. Specific treatment of patients with diabetic nephropathy can be divided into 4 major arenas: cardiovascular risk reduction, glycemic control, blood pressure control, and inhibition of the renin-angiotensin system (RAS). Recommendations for therapy include targeting a hemoglobin A_{1c} concentration < 7% and blood pressure < 140/90 mm Hg with therapy anchored around the use of a RAS-blocking agent. The single best evidence-based therapy for diabetic nephropathy is therapy with a RAS-blocking medication. This Core Curriculum outlines and discusses in detail the epidemiology, pathophysiology, diagnosis, and management of diabetic nephropathy.

Complete author and article information provided before references.

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Epidemiology

Diabetic kidney disease occurs in patients with diabetes mellitus (DM) and reduced kidney function that can be from many diverse causes, including hypertensive nephrosclerosis and unresolved acute kidney failure. Diabetic nephropathy is a diagnosis that refers to specific pathologic structural and functional changes seen in the kidneys of patients with DM (both type 1 and type 2 [T1/T2DM]) that result from the effects of DM on the kidney. These changes result in a clinical presentation that is characterized by proteinuria, hypertension, and progressive reductions in kidney function.

The risk for the development of diabetic nephropathy has a genetic component that is likely polygenetic. The prevalence of diabetic nephropathy varies among racial and ethnic groups such that African Americans (potentially by *APOL1* gene variants), Native Americans, and Mexican Americans have increased risk as compared with European Americans. Although an argument can be made that barriers to care contribute to this discrepancy in prevalence, it is likely not the sole factor, such that genetic differences in these populations must also play a role. Familial studies have demonstrated clustering of diabetic nephropathy. Patients with DM with a first-degree relative with T1/T2DM and diabetic nephropathy have substantially more risk for developing diabetic nephropathy than those without an affected relative. This familial clustering has also been well documented in the Pima Indian population. Ongoing research is attempting to identify specific genetic factors and genes associated with the development of diabetic nephropathy. Although several candidate genes, including glucose transporter 2, transforming growth factor β, and endothelial nitric oxide synthase, have been identified, isolating a definitive causal pathway has proved to be elusive because there is no simple Mendelian inheritance and the interplay of several genes is likely involved and may differ between populations.

Additional Readings

- Family Investigation of Nephropathy and Diabetes Research Group. Genetic determinants of diabetic nephropathy: the Family Investigation of Nephropathy and Diabetes (FIND). *J Am Soc Nephrol.* 2003;14(suppl 2):S202-S204.
- Freedman BI, Bostrom M, Daeihagh P, Bowden DW. Genetic factors in diabetic nephropathy. *Clin J Am Soc Nephrol.* 2007;2:1306-1316.
- Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetic kidney disease in Pima Indians. *Diabetes Care.* 1993;16:335-341.
- Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med.* 1989;320:1161-1165.

Pathophysiology

The pathophysiology leading to the development of diabetic nephropathy and resultant end-stage kidney disease follows from the diabetic milieu leading to the generation and circulation of advanced glycation end products, elaboration of growth factors, and hemodynamic and hormonal changes. These lead to the release of reactive oxygen species and inflammatory mediators. Collectively,

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

these changes result in glomerular hyperfiltration, glomerular hypertension, renal hypertrophy, and altered glomerular composition, which is manifested clinically as albuminuria and hypertension. Pathologically, the kidneys undergo several changes, including deposition (in primarily the mesangium) of extracellular matrix, glomerular basement membrane thickening, proliferative changes, and tubular atrophy, ultimately resulting in interstitial fibrosis and glomerulosclerosis (the final common pathway of many kidney diseases). A schema depicting this process is shown in Figure 1.

With the onset of DM, kidney size and weight increase by an average of 15%, and this size increase remains even after progressive reductions in kidney function occur. An examination of kidney tissue reveals thickening of the glomerular basement membrane and expansion of the mesangium. The classic pathologic lesion of diabetic nephropathy is nodular in nature and was first described by Kimmelstiel and Wilson in 1936. The nodules are typically acellular and positive by periodic acid–Schiff stain. Although these nodules are pathognomonic for diabetic nephropathy, they are reported in only 10% to 50% of biopsy specimens from patients with T1/T2DM. Far more common is the diffuse glomerular lesion that is characterized by diffuse mesangial matrix expansion. Arteriolar lesions involving both the afferent and efferent vessels are also prominent and common in DM. Over time, hyaline material replaces the entire vessel wall structure and this is highly specific for DM. Examples of these lesions are shown in Figure 2. It is important to note that lesions similar to both the nodular and diffuse varieties can be seen in other disease states, such as membranoproliferative glomerulonephritis, amyloidosis, and light-chain deposition disease. Specific stains, immunofluorescence staining, and electron microscopy, as well as the clinical history of the patient, will elucidate the specific diagnosis.

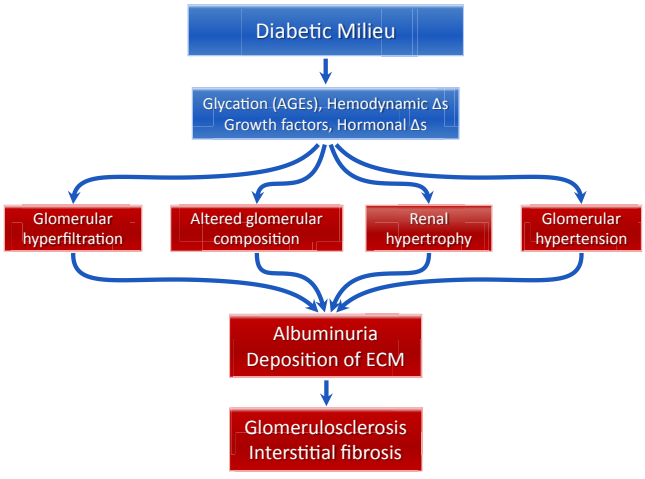


Figure 1. Pathophysiology of diabetic nephropathy. Abbreviations: AGE, advanced glycation end product; ECM, extracellular matrix.

Additional Readings

- Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia.* 1996;39:1569-1576.
- Fioretto P, Steffes MW, Sutherland DE, Mauer M. Sequential renal biopsies in insulin-dependent diabetic patients: structural factors associated with clinical progression. *Kidney Int.* 1995;48:1929-1935.
- Schwartz MM, Lewis EJ, Leonard-Martin T, Lewis JB, Batlle D. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The Collaborative Study Group. *Nephrol Dial Transplant.* 1998;13:2547-2552. ★ **ESSENTIAL READING**

Natural History

Case 1: *A 52-year-old woman with T2DM diagnosed 1 year ago is referred to you for evaluation of proteinuria noted first 3 months ago. Family history is positive for diabetic nephropathy. Physical examination shows blood pressure (BP) of 140/95 mm Hg and normal fundal examination findings and is otherwise unremarkable. Laboratory studies show serum creatinine concentration of 0.9 mg/dL, and urinalysis shows protein (3+) with unremarkable sediment.*

Question 1: Which of the following statements is correct?

a) The finding of proteinuria 6 months after the diagnosis of T2DM is strongly against the diagnosis of diabetic nephropathy.
b) Normal fundal examination findings should strongly suggest an alternative diagnosis.
c) The most likely diagnosis is diabetic nephropathy.
d) Increases in BP in the majority of patients with diabetic nephropathy are seen only after decline in kidney function.

For the answer to the question, see the following text.

The natural history of diabetic nephropathy in patients with T1DM was initially characterized in the late 1970s by Kussman et al by examining death records of patients with juvenile-onset DM who were classified as having died of kidney failure. This analysis resulted in an understanding of the true untreated natural history of diabetic nephropathy due to T1DM as it was before the advent of therapy for this complication of DM. Based on this study, proteinuria appears 11 to 23 years after the T1DM diagnosis, serum creatinine concentration begins to increase after 13 to 25 years, and end-stage kidney disease develops after 18 to 30 years. With the subsequent development of more sensitive assays to detect urinary albumin excretion, small amounts of albumin in the urine (microalbuminuria; 30-300 mg/g creatinine) were noted to precede the development of overt proteinuria (macroalbuminuria; >300 mg/g creatinine) in most patients, occurring 5 to 10 years after the diagnosis of DM. Presently, microalbuminuria and macroalbuminuria are referred to as

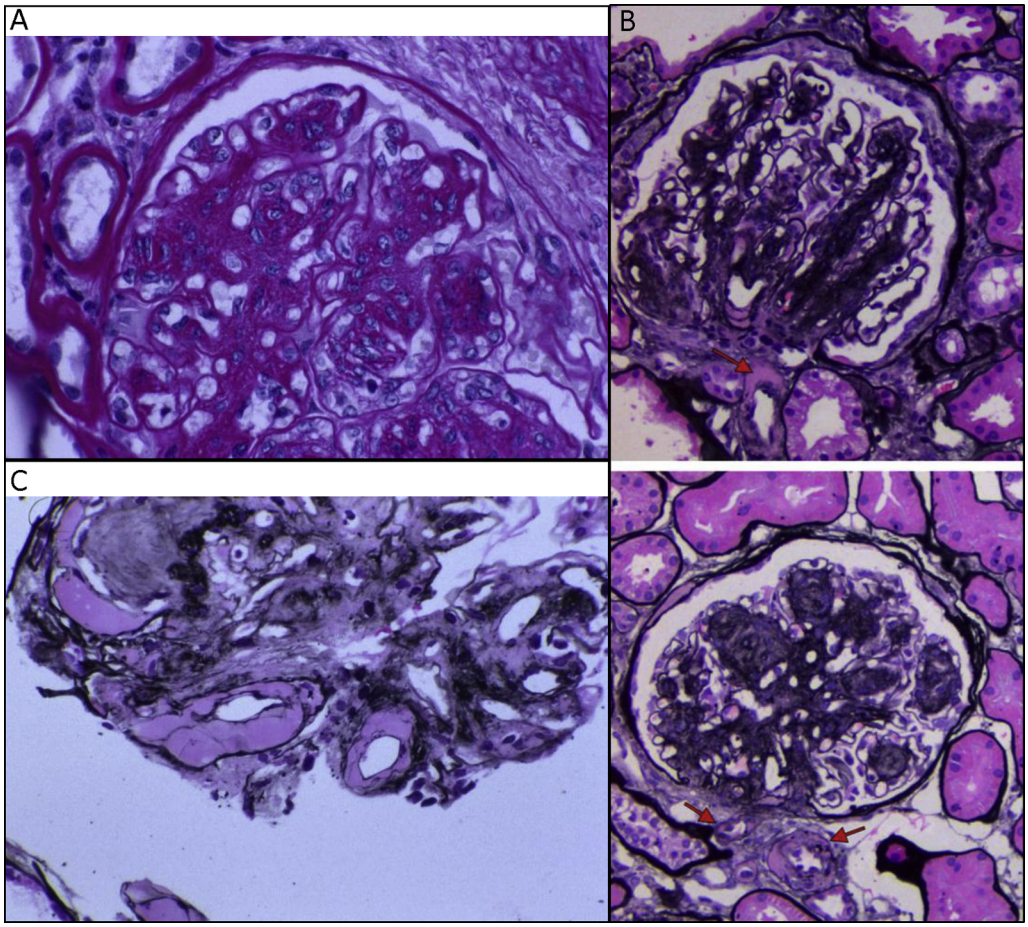
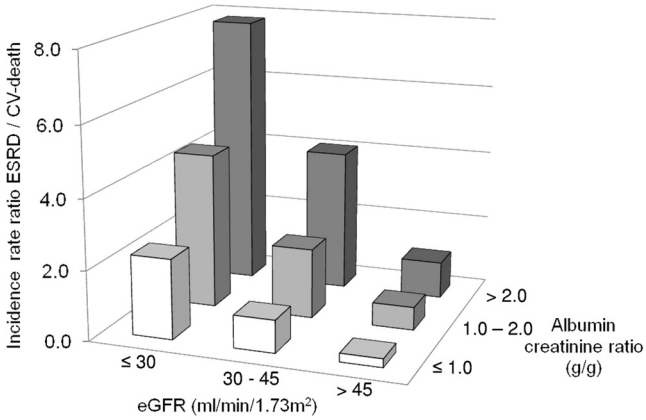


Figure 2. Kidney biopsy images of diabetic nephropathy. (A) Diffuse mesangial matrix expansion, increased mesangial hypercellularity, and prominent glomerular basement membranes in diabetic nephropathy. The basement membrane is uniformly thick without evident deposits (periodic acid–Schiff stain; original magnification, ×400). Reproduced from Fogo (Diabetic nephropathy. *Am J Kidney Dis*. 1999;34(5):E18-E19). (B) Diabetic nephropathy with (top) diffuse mesangial expansion and arteriolar hyalinosis (red arrow) and (bottom) nodular mesangial expansion (Kimmelstiel-Wilson nodules) and concomitant hyalinosis of afferent and efferent arterioles (red arrows; Jones silver stain). Reproduced from Najafian et al (Diabetic nephropathy. *Am J Kidney Dis*. 2015;66(5):e37-e38). (C) Arteriolar hyalinosis: both afferent and efferent arterioles, shown here at the vascular pole, are hyalinized in diabetic nephropathy. This insudation of plasma proteins is due to endothelial injury. In contrast to hypertensive lesions, for which only the afferent arteriole is affected, there is injury to both afferent and efferent arterioles in diabetic nephropathy. (Top left) There is also mesangial matrix expansion and prominent basement membranes and a focus of hyalin within the sclerotic area in the glomerulus (Jones' silver stain; original magnification, ×400). Reproduced from Fogo (Diabetic nephropathy. *Am J Kidney Dis*. 1999;34(5):E18-E19). All images reproduced from the original *AJKD* Atlas of Renal Pathology or the *AJKD* Atlas of Renal Pathology II with the permission of the copyright holder (National Kidney Foundation).

A2 and A3, respectively, by the KDIGO (Kidney Disease: Improving Global Outcomes) chronic kidney disease (CKD) guideline. The natural history of diabetic nephropathy in patients in longitudinally studied populations with T2DM is essentially identical to that in patients with T1DM. However, outside a study situation, the timing of DM onset in patients with T2DM is difficult to assess. Therefore, a patient may even present with proteinuria and on kidney biopsy have diabetic nephropathy before T2DM is diagnosed. Another important difference in the natural history of patients with T1 versus T2DM is that the major macrovascular complication, namely cardiac disease and death due to cardiac disease, can occur at any point along the course of a patient with T2DM from the onset of DM and early diabetic nephropathy, whereas the elevated risk for cardiovascular disease is not apparent until advanced kidney disease has developed in patients with T1DM.

The classic study by Kussman et al in patients with T1DM allows one to picture a timeline of kidney disease progression that starts with microalbuminuria and proceeds sequentially through stages of overt proteinuria, kidney function decline, and ultimately end-stage kidney disease. Multiple studies of diabetic nephropathy

progression over the years have confirmed this timeline and the critical role of proteinuria assessment both as a diagnostic criterion for the presence of diabetic nephropathy and for the assessment of disease severity and likelihood of progression. The single biggest predictor of kidney function deterioration and diabetic nephropathy progression is proteinuria (Fig 3). When the loss of kidney function has begun, as evidenced by an increasing serum creatinine concentration or a declining estimated glomerular filtration rate (eGFR), the patient with diabetic nephropathy begins a continual decline toward chronic kidney failure and renal replacement therapy or death. Based on studies of untreated patients with T1DM and Pima Indians with T2DM, the rate of GFR loss can be on the order of 7 to 12 mL/min/1.73 m^2 per year. Treatment with renin-angiotensin system (RAS) inhibitors has reduced this rate of decline to 3 to 6 mL/min/1.73 m^2 per year (data discussed in detail later in this article). Based on analysis of cohorts of patients with T2DM including those with no nephropathy, early nephropathy, and late nephropathy conducted in the 1980s and 1990s, cardiovascular death was thought to be more frequent than progression of kidney disease to end-stage kidney disease. However, a more recent analysis of participants in 2 large multinational renal clinical trials in patients with established advanced diabetic nephropathy and proteinuria, the risk for end-stage kidney disease was significantly more common than cardiovascular death (incidence rate ratio [IRR], 4.92) and all-cause mortality (IRR, 2.61). It may be that multiple therapies aimed at reducing the complications of DM or cardiovascular disease have sufficiently reduced the rate of macrovascular complications such that more patients progress to end-stage kidney disease.



ACR (g/g)	eGFR (ml/min/1.73m²) ≤30	30 - 45	>45
> 2.0	12.87 (5.97-27.74)	7.46 (3.63-15.33)	7.40 (3.32-16.47)
1.0 – 2.0	7.12 (3.16-16.04)	3.47 (1.63-7.40)	2.80 (1.18-6.64)
≤1.0	3.61 (1.49-8.73)	1.49 (0.64-3.48)	1.00 (reference)

Figure 3. Risk for end-stage kidney disease increases as proteinuria increases and estimated glomerular filtration rate (eGFR) decreases. Incidence rate ratios of end-stage renal disease (ESRD) and cardiovascular (CV) death events by baseline albuminuria and GFR levels. The table below the figure shows the multivariate adjusted risk for ESRD for each albuminuria and eGFR category, accounting for the possibility of competing events between ESRD and CV death. Abbreviation: ACR, albumin-creatinine ratio. Reproduced from Packham et al (Relative Incidence of ESRD Versus Cardiovascular Mortality in Proteinuric Type 2 Diabetes and Nephropathy: Results From the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) Database. *Am J Kidney Dis.* 2012;59(1):75-83) with permission of the copyright holder (National Kidney Foundation).

Recent reports have noted that up to 25% of patients with T2DM and diminished kidney function have little or no proteinuria despite having biopsy-proven diabetic nephropathy. The cause of this change in profile of diabetic nephropathy is unclear. This phenomenon may be due to the impact of long-term RAS-inhibitor therapy, underdiagnosed unresolved acute kidney injury, or other factors impacting on the traditional natural history described earlier. The patient presented here with a strong family history and proteinuria most likely has diabetic nephropathy. The timing of proteinuria is variable in T2DM and can be noted at the time of the diagnosis. Hypertension is a common finding in these patients, often preceding the increase in serum creatinine concentration. Retinopathy as noted is seen in only two-thirds of these patients. Therefore, the correct answer to Question 1 is (c).

Additional Readings

- Dwyer JP, Lewis JB. Nonproteinuric diabetic nephropathy: when diabetics don't read the textbook. *Med Clin North Am.* 2013;97:53-58. ★ ESSENTIAL READING
- Hovind P, Tarnow L, Rossing P, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. *BMJ.* 2004;328:1105-1109.
- Kussman MJ, Goldstein H, Gleason RE. The clinical course of diabetic nephropathy. *JAMA.* 1976;236:1861-1863. ★ ESSENTIAL READING
- Nelson RG, Bennett PH, Beck GJ, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. *N Engl J Med.* 1996;335:1636-1642.
- Packham DK, Alves TP, Dwyer JP, et al. Relative incidence of ESRD versus cardiovascular mortality in proteinuric type 2 diabetes and nephropathy: results from the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) database. *Am J Kidney Dis.* 2012;59:75-83. ★ ESSENTIAL READING

Diagnosis of Diabetic Nephropathy

The approach to a patient with DM and evidence of kidney disease (eg, albuminuria, hematuria, or decreased eGFR) must center on the determination of whether the patient's kidney disease is diabetic nephropathy or

another kidney disease. The natural history and progression timeline discussed earlier will greatly aid the clinician in determining the likelihood that a given patient's disease is diabetic nephropathy in individuals with T1DM. The development of significant albuminuria before 5 years' or after 25 years' duration of T1DM decreases the likelihood of diabetic nephropathy. Additionally, 95% of patients with T1DM and diabetic nephropathy also have diabetic retinopathy, so the absence of retinopathy may imply a diagnosis other than diabetic nephropathy. Seven-field fundus photos must be obtained to eliminate the presence of retinopathy and prompt kidney biopsy because a dilated ophthalmologic examination is insensitive. Unfortunately, patients with T2DM are more challenging because these epidemiologic clues are not as helpful. Diabetic retinopathy is concordant with diabetic nephropathy in only about 60% to 65% of cases; thus, its absence does not generate a high negative predictive value for the diagnosis of diabetic nephropathy. Also, because the onset of T2DM is generally unknown, one cannot as reliably use the natural history timeline to assist in diagnosis. Thus, it is incumbent on the practicing clinician to assess whether something other than DM is the cause of kidney disease. This evaluation will typically involve a thorough history and physical examination and selected laboratory and imaging tests to determine whether a kidney biopsy would be of benefit. There is no formal practice guideline on when to pursue kidney biopsy in patients with DM. Prospective kidney biopsy studies have illustrated that if a patient with DM has retinopathy (T1DM), onset of proteinuria in the usual timeframe (T1DM), and no evidence to support another disease (T1/T2DM), an alternative diagnosis that would substantially alter therapy is unlikely to be found. Therefore, it is not surprising that most patients with DM and reduced kidney function do not undergo kidney biopsy.

Additional Readings

- Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia.* 1996;39:1569-1576.
- Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes.* 1990;39:1116-1124.
- Schwartz MM, Lewis EJ, Leonard-Martin T, Lewis JB, Batlle D. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The Collaborative Study Group. *Nephrol Dial Transplant.* 1998;13:2547-2552.

Treatment of Diabetic Nephropathy

Specific treatment of patients with diabetic nephropathy can be divided into 4 major arenas: cardiovascular risk reduction, glycemic control, BP control, and inhibition of the RAS. We take each of these in turn with case-based examples to discuss the optimal evidence-based approach to care of patients with diabetic nephropathy.

Cardiovascular Risk Reduction

Patients with diabetic nephropathy necessarily have DM and thus cardiovascular disease risk is significant and a competing risk for kidney failure. Therefore, it is important to ensure that aggressive risk factor modification is undertaken, usually in partnership with the patient's primary care physician. Components of this therapeutic approach include tobacco cessation and lipid-lowering therapy. Evidence of cardiovascular disease risk reduction for both tobacco cessation and lipid lowering is abundant and thorough discussions can be found elsewhere. Unfortunately, because data are scant for the effects of these therapies to modify the course of kidney disease, it is outside the scope of this review.

Glycemic Control

Case 2: *A 48-year-old obese African-American woman with T2DM presents to your office for follow-up. She is presently using metformin, 500 mg, twice daily and lisinopril, 20 mg, daily. BP is 129/74 mm Hg and physical examination findings are otherwise unremarkable. Key laboratory values include the following: potassium, 4.7 mEq/L, serum creatinine, 0.9 mg/dL; albumin-creatinine ratio, 400 mg/g; and glycated hemoglobin (HbA_{1c}), 9.1%.*

Question 2: Based on the evidence, what should the goal HbA_{1c} concentration be for this patient?

a) As close to 6% as possible.
b) Around 7%.
c) Between 8% and 9%.
d) There is no relationship between HbA_{1c} and microvascular outcome.

For the answer to the question, see the following text.

The effect of improved glycemic control on clinical outcomes, including progression of diabetic nephropathy, has been tested in multiple large clinical trials involving patients with T1/T2DM. The principal evidence regarding the benefit of glycemic control in patients with T1DM comes from the Diabetes Control and Complications Trial (DCCT). This seminal trial, conducted from 1983 to 1993 in the United States and Canada, randomly assigned 1,441 patients to intensive (goal $HbA_{1c} < 6.05\%$) versus conventional glycemic control with insulin with follow-up for a mean of 6.5 years. Median HbA_{1c} concentration was 9.1% versus 7.3% for conventional versus intensive control. Intensive control resulted in a relative risk reduction of 39% for the development of microalbuminuria and relative risk reduction of 56% for overt proteinuria. Intensive glycemic control was also associated

Table 1. Summary of Key Glycemic Control Trials

Trial	Population	N	Intervention Target	Achieved Intervention	Findings in Intensive Care Group	Comments
DCCT	T1DM	1,441	Intensive therapy targeting fasting and postprandial blood glucose vs conventional therapy	HbA_{1c} 7.3% vs 9.1%	Decreased microvascular complications (including microalbuminuria, proteinuria, retinopathy, and neuropathy)	
EDIC	T1DM	1,375 patients that completed DCCT	Observational follow-up of DCCT with all getting intensive therapy	HbA_{1c} 7.8% vs 7.9%	Reduction in microalbuminuria and proteinuria	
UKPDS	Newly Diagnosed T2DM	3,867	Intensive therapy targeting a fasting blood glucose vs conventional therapy	HbA_{1c} 7% vs 7.9%	Reduction in any diabetes-related end point in aggregate	Reduction not seen in kidney-specific events (microalbuminuria, proteinuria, or doubling of Scr)
ACCORD	T2DM and CV event history or risk	10,251	HbA_{1c} < 6.0% vs 7%-7.9%	HbA_{1c} 6.4% vs 7.5%	Increased CV and total mortality	No benefit on kidney end points
ADVANCE	T2DM and CV event history or risk	11,140	HbA_{1c} < 6.5% vs routine care	HbA_{1c} 6.3% vs 7.0%	No benefit on CV outcomes; reduction in microvascular events	Albuminuria reduced by 21%
VADT	T2DM and poor BP control	1,791	Reduction in HbA_{1c} of 1.5% vs routine care	HbA_{1c} 6.9% vs 8.4%	No benefit	No benefit on kidney end points

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HbA_{1c}, hemoglobin A_{1c}; Scr, serum creatinine; T1(2)DM, type 1 (2) diabetes mellitus; UPKDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

with reductions in other microvascular complications, namely retinopathy and neuropathy. After the trial ended, 1,375 participants volunteered to continue in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Given the benefits seen with the intensive control arm in the DCCT, all participants were advised to remain or convert to intensive control. Thus, glycemic control as measured by HbA_{1c} concentration converged to 7.8% and 7.9% for the former conventional and former intensive control groups, respectively. Despite this convergence, the development of microalbuminuria and overt proteinuria was reduced (53% and 86%, respectively) by intensive control over 4 additional years of follow-up. Thus, the beneficial effects of glycemic control on microvascular complications are significant and durable in patients with T1DM.

The available data for patients with T2DM are more ambiguous. In the United Kingdom Prospective Diabetes Study (UKPDS), participants were randomly assigned to intensive glycemic control using oral agents and/or insulin or to conventional therapy (diet control). The achieved mean HbA_{1c} concentration was 7.0% in the intensive control arm compared to 7.9% in the conventional arm. Participants in the intensive control arm saw a reduction in any DM-related end point, but a reduction was not seen for specific kidney events of interest, namely the development of microalbuminuria, overt proteinuria, or doubling of serum creatinine concentration. Three more recent large trials with an aggregate enrollment of nearly 25,000 participants were conducted to assess any potential benefit of intensive glucose control in T2DM: ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (VA Diabetes Trial). These studies targeted and achieved HbA_{1c} concentrations of ~6.0% relative to a control arm of ~7.0%. Results of these studies are decidedly mixed, with either no benefits on cardiovascular effects ranging to cardiovascular risk in the intensive group and no kidney benefit, with the exception of 1 trial showing a reduction in albuminuria but no benefit on the preservation of kidney function. All 3 trials established increased risk for hypoglycemic events related to intensive glycemic control to HbA_{1c} concentrations of near 6.0%. Intensive glycemic control to an HbA_{1c} concentration of 7.0% prevents microvascular (not macrovascular) complications (UKPDS). However, it is unclear whether any further HbA_{1c} concentration reduction is of utility, particularly for preventing kidney disease outcomes.

Based on the available evidence (summarized in Table 1), the patient presented earlier should have her glycemic control therapy intensified, targeting a goal HbA_{1c} concentration of 7.0% to reduce microvascular complications and diabetic nephropathy progression (thus [b] is the correct choice for Question 2). Any further

reduction is of unproven benefit and would likely put the patient at risk for hypoglycemic events. This is congruent with current American Diabetes Association and KDOQI clinical practice guidelines.

Additional Readings

- Action to Control Cardiovascular Risk in Diabetes Study G; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545-2559. ★ ESSENTIAL READING
- ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358:2560-2572. ★ ESSENTIAL READING
- Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
- Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360:129-39. ★ ESSENTIAL READING
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-853. ★ ESSENTIAL READING
- Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA.* 2002;287:2563-2569.

BP Control

Case 3: *A 52-year-old white man with T2DM complicated by retinopathy, neuropathy, and stage 3 CKD due to diabetic nephropathy comes in to your office for routine follow-up care. He is presently treated with insulin and lisinopril, 40 mg, daily. BP is 150/95 mm Hg and the rest of the examination findings are unremarkable. Key laboratory values include the following: serum potassium, 4.7 mEq/L; serum creatinine, 1.5 mg/dL; albumin-creatinine ratio, 800 mg/g; and HbA_{1c}, 7.1%.*

Question 3: Based on the evidence, what should the goal BP be for this patient?

a) Although lower BP decreases cardiovascular events, it has no impact on clinically meaningful renal outcomes.
b) Less than 140/90 mm Hg.
c) As low as tolerated, but > 110/70 mm Hg.
d) It depends on the patient's age, with a goal of <150/95 mm Hg in patients older than 65 years.

For the answer to the question, see the following text.

Many well-designed randomized controlled trials have demonstrated the cardiovascular benefit of lowering systolic BP to <140 mm Hg. However, many of these trials specifically excluded patients with CKD. Observational studies have linked the presence of hypertension to the development of microalbuminuria, overt proteinuria, and declining kidney function, with higher BP associated with worse outcomes in a continuous fashion. Observational data from 2 randomized clinical trials testing an intervention in patients with T2DM, IDNT (Irbesartan Diabetic Nephropathy Trial) and the RENAAL (Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan) trial are known for demonstrating the benefit of angiotensin receptor blockers (ARBs) to delay the progression of kidney disease (discussed in detail later in this article), and an analysis of BPs through the course of the trials yields useful information. Participants in these 2 trials were not randomly assigned to different levels of BP control. However, in subsequent analyses, it was clear that participants with poor BP control at entry did worse relative to their better-controlled counterparts. Additionally, achieved BP was a stronger predictor of kidney outcome than entry BP. Thus, BP control is of paramount importance. The effect of achieved BPs was analyzed in detail in IDNT and suggested the presence of a J-shaped curve such that kidney benefit reached a plateau at systolic BP < 130 mm Hg, and all-cause mortality increased at systolic BP < 120 mm Hg.

In studies looking specifically at randomly assigning participants to 2 different levels of BP control, the UKPDS examined the impact of randomly assigning participants to 2 different levels of BP control on microvascular and macrovascular complications. During a mean 8.4 years of follow-up, achieved mean BPs in the 2 groups were 144/82 versus 154/87 mm Hg. The risk for any DM-related complication, death, adverse cardiovascular events, and the composite of microvascular events was substantially decreased in the lower BP arm. The study did not demonstrate benefit on the kidney outcomes (proteinuria and kidney function decline), but the study was not designed to carefully or frequently assess kidney outcomes. The benefits of BP control below a systolic BP of 140 mm Hg have been more difficult to demonstrate. The ABCD (Appropriate Blood Pressure in Diabetes) trial randomly assigned 480 participants with T2DM to intensive (achieved BP ~128/75 mm Hg) versus moderate (achieved BP ~137/81 mm Hg) control with follow-up for 5 years. The study noted a decrease in the development of microalbuminuria and overt proteinuria in the intensive BP group, but was unable to demonstrate a benefit on creatinine clearance, the primary outcome of the trial.

The landmark ACCORD trial tested the hypothesis that more intensive BP control (systolic BP < 120 mm Hg) would be of benefit relative to standard BP therapy (systolic BP < 140 mm Hg), with 4,733 patients participating in this randomized trial. The achieved systolic BPs at 1 year

of follow-up were widely separated, at 119.3 and 133.5 mm Hg in the 2 groups. It took on average 3.5 BP medications to achieve this BP goal in the intensive therapy group versus 2.3 BP medications in the standard therapy group. The study found no reduction in the rate of the primary composite cardiovascular outcome associated with either BP goal. Intensive BP control was associated with a reduction in albuminuria but no reduction was seen in end-stage kidney disease events. It is important to note that the ACCORD trial was not powered to detect renal events because the trial population was a more general cohort with DM rather than one selected for diabetic kidney disease. Increased risk for acute kidney injury events requiring dialysis therapy along with other adverse events attributed to antihypertensive therapy were also seen in the intensive BP control arm.

Based on the current evidence, it is clear that BP reduction is important in the management of patients with diabetic nephropathy. Cardiovascular and kidney event rates are higher with increasing BP and are reduced progressively with therapy to lower BP. There may be a point beyond which further BP reduction may not be helpful or even be harmful despite a reduction in proteinuria. The current KDOQI guideline recommends a goal BP < 130/80 mm Hg, whereas the Eighth Joint National Committee (JNC 8) guidelines recommend a goal BP < 140/90 mm Hg for most patients with T2DM and diabetic nephropathy, but with individualization. Based on our assessment of the evidence, for the patient described above, we recommend that further intensification of antihypertensive therapy should be undertaken with a goal BP < 140/90 mm Hg (thus [b] is the correct answer to Question 3). One should expect to add 1 to 2 BP medications at full dose to his regimen to achieve this objective.

Additional Readings

- ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575-1585. ★ **ESSENTIAL READING**
- Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol.* 2005;16:2170-2179. ★ **ESSENTIAL READING**
- Eijkelkamp WB, Zhang Z, Remuzzi G, et al. Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. *J Am Soc Nephrol.* 2007;18:1540-1546.
- Pohl MA, Blumenthal S, Cordonnier DJ, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the Irbesartan Diabetic Nephropathy Trial: clinical implications and limitations. *J Am Soc Nephrol.* 2005;16:3027-3037.
- Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int.* 2002;61:1086-1097.
- Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ.* 1998;317:703-713.

RAS Inhibition

Case 4: *A 45-year-old African American man presents for initial evaluation in the nephrology clinic. He has had T2DM for 7 years and it has been well controlled. He also reports hypertension for the past 5 years, and it has been under good control. BP is 135/75 mm Hg. Physical examination notable for lower-extremity edema (1+) to the mid-shin. Findings are otherwise unremarkable. His BP is managed with metformin, 1,000 mg, twice daily and chlorthalidone, 25 mg, daily. Key laboratory values are as follows: serum potassium, 4.1 mg/dL; serum creatinine, 1.3 mg/dL; albumin-creatinine ratio, 1,257 mg/g; and HbA_{1c}, 6.9%.*

Question 4: What should be added to his regimen to slow the progression of diabetic nephropathy?

a) Add an ARB to the regimen with goal of decreasing proteinuria.
b) His BP is well controlled, so continue on the same regimen.
c) Switch chlorthalidone to furosemide, given the elevated creatinine concentration.
d) Add both an ARB and an angiotensin-converting enzyme (ACE) inhibitor, with the goal of decreasing proteinuria to protein excretion < 300 mg/d.

RAS blockade using various drugs, including ACE inhibitors, ARBs, direct renin inhibitors, and mineralocorticoid antagonists have shown efficacy in animal models of diabetic nephropathy across the full spectrum of DM-related injury. In humans, RAS inhibition has proved to be the single most effective therapy for slowing the progression of diabetic nephropathy. These agents have been studied at each clinical stage of diabetic nephropathy, and we review those data here.

RAS blockade has been studied in patients with T1/T2DM without microalbuminuria to assess whether therapy can prevent its development. Multiple trials in patients with T1DM (RASS [Renin-Angiotensin System Study], DIRECT [Diabetic Retinopathy Candesartan Trial]-Prevent 1, and DIRECT-Protect 1) failed to show a benefit of therapy to prevent the development of microalbuminuria. These results suggest that early therapy in patients with T1DM is ineffective in preventing the development of microalbuminuria.

This treatment strategy has also been tested in patients with T2DM with mixed results. The use of ramipril in the HOPE (Heart Outcomes Prevention Evaluation) trial was not effective for this purpose. BENEDICT (the Bergamo Nephrologic Diabetes Complications Trial) randomly assigned patients to 1 of 4 arms (placebo, trandolapril, verapamil, or trandolapril plus verapamil) for at least 3 years with a goal BP < 120/80 mm Hg. The 2 arms containing trandolapril showed a benefit in preventing the

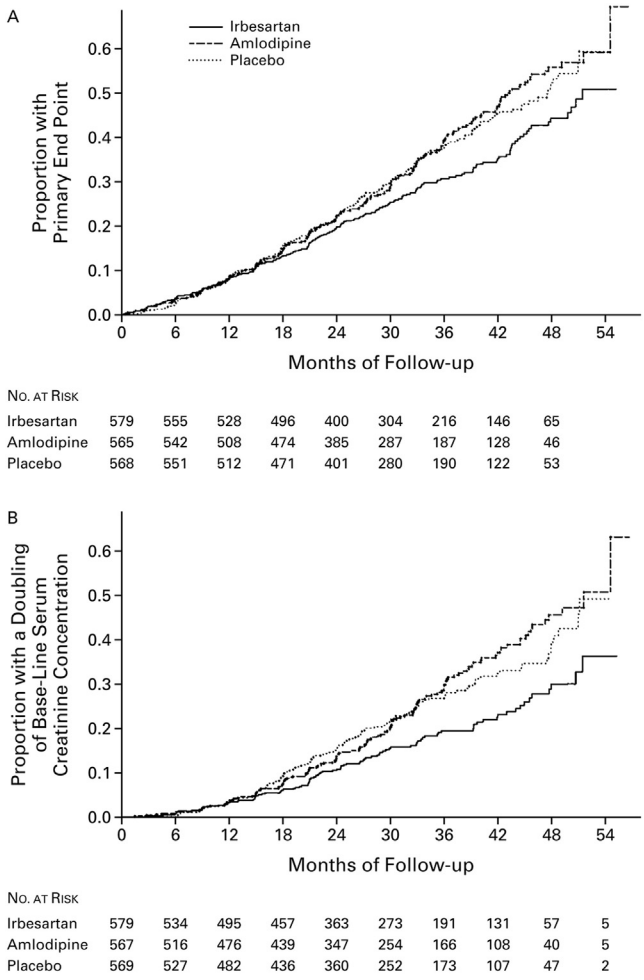


Figure 4. Cumulative proportions of patients with the primary composite end point (A) and its components, a doubling of the base-line serum creatinine concentration (B). Irbesartan reduces the risk for the composite outcome of doubling of serum creatinine concentration, end-stage kidney disease, or death as compared to amlodipine or placebo. Reproduced from Lewis et al (Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. *New Engl J Med.* 2001;345:851-860) with permission of the copyright holder (Massachusetts Medical Society).

development of albuminuria, with post hoc analyses suggesting that the effect was independent of BP reduction. Last, the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) trial followed up 4,449 participants for a median of 3.2 years. There was a statistically significant follow-up difference in BP between the olmesartan and placebo arms. The primary analysis of the trial showed that olmesartan prevented or delayed the onset of microalbuminuria, with microalbuminuria developing in 8.2% versus 9.8% of participants (olmesartan vs placebo). The olmesartan group had lower BPs and an increase in cardiovascular deaths. Thus, RAS blockade may prevent the development of microalbuminuria in patients with T2DM.

The next stage along the timeline is the transition of a patient with microalbuminuria to overt proteinuria. Treatment with the ARB irbesartan was investigated for its ability to prevent the development of overt proteinuria in patients with T2DM and microalbuminuria in the IRMA-2 (Effect of Irebesrtan in the Development of Diabetic Nephropathy in Patients With T2DM) trial. This trial randomly assigned 590 patients with T2DM and microalbuminuria to irbesartan, 150 mg, daily; irbesartan, 300 mg, daily; or matching placebo with follow-up for 2 years. Irbesartan reduced the risk for the development of overt proteinuria (defined here as albumin excretion > 200 mg/d) in the intent-to-treat group as a whole. Examining the subgroups, a dose-dependent benefit was suggested, with hazard ratios (HRs) of 0.3 ($P < 0.001$) in 300-mg group and 0.61 ($P = 0.08$) in the 150-mg group.

The first large trial to examine the effect of ACE inhibitors on the progression of advanced diabetic nephropathy randomly assigned 409 patients with T1DM, overt proteinuria (protein excretion ≥ 500 mg/d), and reduced kidney function (serum creatinine ≤ 2.5 mg/dL) to captopril, 25 mg, 3 times a day or matching placebo. Participants in this trial could receive other antihypertensive medications to achieve BP control. There was a 48% reduction in risk for doubling of serum creatinine concentration and a 50% reduction in the composite end point of death, dialysis therapy, or transplantation. This trial established the efficacy of ACE inhibitors independent of BP control in slowing the progression of diabetic nephropathy in patients with T1DM and overt proteinuria.

IDNT and the RENAAL study investigated the effect of 2 ARBs (irbesartan and losartan, respectively) on the progression of diabetic nephropathy in patients with T2DM, overt proteinuria, and reduced kidney function. IDNT randomly assigned 1,715 participants to irbesartan, amlodipine, or placebo with follow-up for a mean of 2.6 years. BP was targeted at < 135/85 mm Hg and was achieved with agents in classes other than those under study. Independent of BP control, irbesartan reduced the risk for the composite outcome of doubling of serum creatinine concentration, end-stage kidney disease, or death as compared to amlodipine or placebo (Fig 4). The RENAAL trial followed up 1,513 patients with T2DM and overt proteinuria for a mean of 3.4 years and demonstrated that losartan, 100 mg, daily was superior to placebo to reduce the risk for the same composite end point as in IDNT. Taken together, these studies provide robust evidence supporting the benefit independent of BP control of RAS-blocking medication on slowing the progression of diabetic nephropathy. Although these trials showed a dramatic benefit with ARB therapy, many participants on ARB therapy still had renal events, so there is still great room for further therapy and drug development to derive further benefit. A reduction in proteinuria strongly predicts and is associated with preservation of kidney function in patients treated with ARBs, but not all participants who had a

Table 2. Summary of Key Renin-Angiotensin System Inhibition Trials

Trial	Population	N	Intervention	Conclusions	Comments
ROADMAP	T2DM without microalbuminuria	4,449	Olmesartan vs placebo	Olmesartan delayed the onset of microalbuminuria	Olmesartan group had lower BPs and more CV deaths
IRMA-2	T2DM and microalbuminuria	590	Irbesartan 150 mg vs irbesartan 300 mg vs placebo	Irbesartan reduced the development of overt proteinuria	Subgroup analysis suggested a dose-dependent effect
Captopril Trial	T1DM with proteinuria	409	Captopril 25 mg 3×/d vs placebo	Captopril reduced the risk for doubling of SCr as a primary outcome and death, dialysis therapy, or transplantation as a secondary outcome	
IDNT	T2DM with proteinuria and reduced kidney function	1,715	Irbesartan vs amlodipine vs placebo	Irbesartan reduced the risk for doubling of SCr, ESRD, or death	
RENAAL	T2DM with proteinuria and reduced kidney function	1,513	Losartan vs placebo	Losartan reduced the risk for doubling of SCr, ESRD, or death	
ONTARGET	Patients with CV risk	25,620	Ramipril vs telmisartan vs telmisartan and ramipril	No CV benefit among the 3 arms; proteinuria reduction in combination therapy arm	Increase in "DDT" events in combination therapy arm
VA NEPRON-D	T2DM and proteinuria	1,448	Losartan and lisinopril vs losartan and placebo	Trial terminated early due to AKI events and hyperkalemia in combination therapy arm	
ALTITUDE	T2DM, proteinuria, and CV risk	8,561	ACEi or ARB and aliskiren vs ACEi or ARB and placebo	Trial terminated early due to increase in adverse events and no apparent benefit in the dual-therapy arm	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ALTITUDE, Aliskiren Trial in T2DM Using Cardio-Renal Endpoints; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; DDT, doubling of serum creatinine, dialysis, or transplantation; ESRD, end-stage renal disease; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, Effect of Irebesrtan in the Development of Diabetic Nephropathy in Patients With T2DM; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint; RENAAL, Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCr, serum creatinine; T1(2)DM, type 1(2) diabetes mellitus; VA-NEPHRON-D, Veterans Affairs Nephropathy in Diabetes.

reduction in proteinuria had preserved kidney function and some who had a benefit did not have a reduction in proteinuria.

If some RAS blockade is good, as noted earlier, is more better? The question of therapy with multiple agents that block the RAS was addressed in 3 large clinical trials. The first was ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint), a cardiovascular outcomes trial that randomly assigned 25,620 patients with cardiovascular disease risk to ramipril, telmisartan, or both. There was no difference among the 3 arms in the composite cardiovascular outcome. Notably, there were 9,612 participants with diabetes and 2,781 with microalbuminuria in the trial. Post hoc analysis of kidney outcomes showed a proteinuria benefit in the combination therapy arm. However, there was a significant increase in the renal end point (doubling of serum creatinine, dialysis therapy, or death) in the combination therapy arm compared with the single-agent arms. This increase in the renal end point was primarily driven by the need for urgent dialysis. Although not designed as a kidney outcomes trial, this raised questions about the potential harm of combination therapy. The VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) study randomly assigned 1,448 participants with T2DM and overt proteinuria to either losartan, 100 mg, daily in combination with lisinopril, 40 mg, daily or losartan, 100 mg, daily plus placebo. This trial was terminated early due to an increase in adverse events (acute kidney injury and hyperkalemia) in the combination therapy arm. ALTITUDE (Aliskiren Trial in T2DM Using Cardio-Renal Endpoints) tested whether dual RAS blockade with aliskiren and either an ACE inhibitor or an ARB reduced cardiovascular and kidney events. This trial was also terminated early due to an increase in adverse events and no apparent benefit in the dual-therapy group.

The current evidence (summarized in Table 2) strongly supports the use of RAS-blocking agents in the treatment of patients with diabetic nephropathy. Although RAS blockade with more than 1 agent may be effective in reducing proteinuria, the adverse-event profile (hyperkalemia, acute kidney injury, and increased cardiovascular events) and no benefit in preventing end-stage kidney disease preclude its general use for the treatment of diabetic nephropathy. The patient in case 4 has overt proteinuria with a history consistent with the diagnosis of diabetic nephropathy. The patient could benefit from additional BP control but more importantly has overt proteinuria and is presently not treated with a

RAS-blocking agent; thus, (a) is the correct answer to Question 4. The available evidence supports the addition of an ARB to his regimen for slowing the progression of diabetic nephropathy and additional BP control.

Additional Readings

- Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861-869. ★ ESSENTIAL READING
- Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med.* 2013;369:1892-1903.
- Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med.* 2011;364:907-917.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-1462. ★ ESSENTIAL READING
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851-860. ★ ESSENTIAL READING
- Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet.* 2008;372:547-553.
- Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med.* 2012;367:2204-2213.
- Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001;345:870-878.

Emerging Therapies

The single best evidence-based therapy for diabetic nephropathy is therapy with a RAS-blocking medication, the evidence for which was presented in detail earlier and summarized in Table 2. Since the approval of ARB therapy for the treatment of diabetic nephropathy in patients with T2DM approximately 15 years ago, there has not been a new medication approved by the US Food and Drug Administration for the therapy of diabetic nephropathy. Research has focused on additional therapy to forestall the progression of diabetic nephropathy. Clinical trials have been modeled on the idea of a RAS-blocking medication plus an additional agent. Multiple therapies targeting various proposed molecular mechanisms of injury, including inflammation, fibrosis, and extracellular matrix deposition, have been attempted with marginal success to date. The third-generation mineralocorticoid receptor antagonist finerenone has shown albuminuria reduction in diabetic nephropathy at 90 days without a significant safety concern. Ongoing clinical trials will determine whether the reduction in albuminuria will translate into long-term success in forestalling the progression of diabetic nephropathy and the development of end-stage kidney disease.

Sodium glucose cotransportor 2 (SGLT2) inhibitors are relatively new medications that have been approved for the treatment of diabetes. Their mechanism of action is to block glucose and sodium uptake in the proximal tubule, thereby generating naturesis and glucosuria. Recently, 2 studies, designed as cardiovascular safety studies, EMPA-REG Outcome (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) and CANVAS (Canagliflozin Cardiovascular Assessment Study) have demonstrated significant cardiovascular risk reduction when used for the treatment of diabetes. In these cardiovascular outcome trials, the SGLT2 inhibitors had positive effects on kidney outcomes, namely albuminuria reduction and a reduction in the occurrence of a composite renal outcome. In the EMPA-REG Outcome trial, the HR in the empagliflozin arm for incident or worsening nephropathy (a composite of the development of albuminuria with albumin excretion > 300 mg/g creatinine, doubling of serum creatinine accompanied by eGFR ≤ 45 mL/min, initiation of renal replacement therapy, or death from renal causes) was 0.61 (95% confidence interval [CI], 0.53-0.70; $P < 0.001$). CANVAS demonstrated a benefit of similar magnitude (HR, 0.60; 95% CI, 0.47-0.77) on a composite outcome of a sustained 40% reduction in eGFR, need for renal replacement therapy, or death from renal causes. Although these renal benefits are dramatic, it is important to keep in mind that they are secondary outcomes in trials principally designed to assess cardiovascular safety. There are multiple ongoing dedicated kidney outcome trials, including CREDANCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; ClinicalTrials.gov identifier NCT02065791) using canagliflozin and DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; ClinicalTrials.gov identifier NCT03036150) using dapagliflozin, testing the efficacy of SGLT2 inhibitors to slow the progression of diabetic nephropathy. The results of these dedicated kidney outcome trials are needed before SGLT2 inhibitors can be adopted as therapy to forestall the progression of diabetic nephropathy. Last, other interventions presently under investigation for the therapy of diabetic nephropathy include uric acid–lowering and bicarbonate therapy.

Additional Readings

- Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA.* 2015;314:884-894.
- Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation.* 2016;134:752-772.
- Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;17;377:644-657. ★ ESSENTIAL READING

► Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375:323-334. ★ ESSENTIAL READING

► Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117-2128.

Additional Therapeutic Considerations

In addition to cardiovascular risk reduction, glycemic control, BP control, and inhibition of the RAS, there are some unique issues to consider in the management of a patient with diabetic nephropathy. Thirty percent to 45% of insulin is metabolized and cleared by the kidneys. Therefore, as kidney function decreases, insulin lasts longer, putting patients at risk for hypoglycemic episodes. Additionally, most oral hypoglycemic medications are metabolized and cleared by the kidney. Thus, doses of these agents and insulin must often be reduced as kidney function decreases. Additionally, if hypoglycemia occurs, it may last for a prolonged period that may necessitate hospitalization for observation. Metformin in contraindicated in patients with eGFRs < 30 mL/min/1.73 m^2 due to its association with severe lactic acidosis in these patients. Care must also be taken with dose adjustments for many of the newer oral and injectable diabetes therapies. Last, 2 classes of these newer agents, namely dipeptidyl peptidase 4 (DPP-4) and SGLT2 inhibitors, have demonstrated cardiovascular disease benefit. One should be familiar with these agents and their dosing in patients with reduced kidney function (several are cleared by the kidney or have restrictions on use based on eGFR) because they are likely to be used more for glycemic control in the coming years given their additional benefits.

As stated, cardiovascular risk reduction is of paramount importance in these patients. Lipid-lowering therapy is crucial for cardiovascular risk reduction. There are few studies showing benefit with respect to kidney disease progression, though a meta-analysis of the data in totality suggests some benefit.

The most common cause of type IV renal tubular acidosis is DM. Therefore, patients with diabetic nephropathy at any level of kidney function are at increased risk for hyperkalemia and metabolic acidosis. This specific tubular transport defect can be treated with a low-potassium diet, diuretics, and base supplementation. Treatment of this condition can be critical to allow these patients to receive continuous uninterrupted therapy with RAS-blocking medication that would otherwise be dose limited or precluded altogether due to hyperkalemia.

Patients with diabetic nephropathy are also at increased risk for developing acute kidney injury from iodinated radiocontrast administration, volume depletion, or nonsteroidal anti-inflammatory drug use. Because acute kidney injury can hasten a patient's progression to end-stage kidney disease, care must be taken to avoid or minimize these nephrotoxic exposures. Last, diabetes is also a known risk factor for arteriovenous fistula maturation failure. As with all patients with stage 4 CKD, dialysis access planning is vitally important.

Article Information

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