

# Diabetic Nephropathy

**Ralph Rabkin, MD**

Professor of Medicine, Emeritus  
Department of Medicine  
Division of Nephrology  
Stanford University  
Stanford, California

*As the epidemic of diabetes spreads so does the number of patients at risk for developing diabetic nephropathy, which occurs in 20% to 40% of all diabetic patients. Indeed, diabetes is the most common cause of end-stage renal disease (ESRD) in the United States, accounting for > 40% of patients starting renal replacement therapy each year. Unfortunately, the outcome for diabetic patients with ESRD is worse than that for nondiabetic patients because of comorbid conditions in the diabetic population. However, with early and intensive blood glucose and blood pressure control—including the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers—the development and progression of diabetic kidney disease can be slowed.*

## INCIDENCE AND PREVALENCE

Diabetic kidney disease is the most frequent cause of end-stage renal disease (ESRD) in the United States, Europe, and Japan. According to the US Renal Data System, in 1999 diabetes was the cause of renal failure in 43% of all ESRD patients commencing dialysis therapy, an incidence rate of 136 per million population (1). Because of the multiple comorbid conditions in this group of ESRD patients, especially cardiac and cerebrovascular disease, their morbidity and mortality rates are higher than those in nondiabetic patients. For example, the 3-year mortality rate of patients receiving hemodialysis treatment because of diabetic kidney disease exceeds the rate for ESRD due to hypertension by 26% and for ESRD due to glomerulonephritis by 72% (1). Not surprisingly, the annual cost of caring for diabetic patients with ESRD exceeds that for nondiabetic patients. Overall, the treatment of ESRD in the United States is costly, and the annual expenditure exceeds \$18 billion.

Unfortunately, the incidence of diabetic nephropathy as a cause of ESRD is increasing each year. This increase can be attributed to an increase in the occurrence of diabetes, especially type 2 diabetes; the extended life span of diabetic patients

## KEY POINT

**Diabetic kidney disease is the most frequent cause of ESRD in the United States and treatment of ESRD is costly, exceeding \$18 billion annually.**

due to improved management of comorbid conditions; and the acceptance of patients for replacement therapy who in the past were excluded (2,3). Nephropathy develops in about 20% to 40% of all diabetic patients, although a somewhat lower percentage of those with type 2 diabetes progresses to ESRD, perhaps in part because these patients are older and die from cardiovascular complications. Nevertheless, patients with type 2 diabetes account for more than half the diabetic patients reaching ESRD because of the greater prevalence of type 2 diabetes (1).

Although the prevalence of diabetic nephropathy has been increasing, the last decade has seen significant advances in our understanding

of the pathogenesis and management of the disease. With earlier and more intensive glycemic and blood pressure control, the introduction of potent drugs that interrupt the generation or action of angiotensin II (AII), and the use of other agents that affect vascular biology, the development and progression of diabetic nephropathy can now be slowed.

## NATURAL HISTORY OF DIABETIC NEPHROPATHY

There are several clinical similarities between diabetic nephropathy in patients with type 1 diabetes and in patients with type 2 diabetes; however, the clinical course differs in some respects between these 2 groups. In patients with type 1 diabetes, the onset of diabetes is abrupt and usually occurs at a young age, and in those in whom nephropathy develops the clinical course is relatively well defined (4). Nephropathy usually becomes clinically evident after 15 to 25 years of diabetes and almost inevitably leads to ESRD.

In contrast, because of the insidious onset of type 2 diabetes and the advanced age of the patients, and thus the common presence of coexisting vascular disease and hypertension, early renal involvement is frequently missed. In patients with type 2 diabetes, it is not always clear whether renal failure is due solely to or even caused by diabetes (5). Also, because of the shortened life span of individuals with type 2 diabetes, full-blown manifestations of diabetic nephropathy often are not expressed. Thus, the clinical course of diabetic nephropathy is best defined in type 1 diabetes and proceeds through several stages (**Table I**), which can be modified by therapy (4,6).

Soon after the onset of type 1 diabetes, the kidneys hypertrophy and renal blood flow (RBF) and the glomerular filtration rate (GFR) increase. Over the ensuing 5 to 15 years, the GFR remains elevated or falls within normal range, and there is no elevation in systemic blood pressure. About a decade after diabetes onset, small amounts of albumin, detectable only by sensitive antibody-based assays, appear in the urine (microalbuminuria) of a substantial fraction of patients. After 1 to 5 years of microalbuminuria, larger amounts of protein appear in the urine, which occurs in 30% to 45% of these patients by 10 years (27). This macroalbuminuria is detectable by the urine dipstick method. At this time blood pressure is usually elevated and renal function begins to decline. The rate of decline in function varies considerably among patients but averages 1 mL/min per month in patients not receiving renoprotective therapy. Typically ESRD is reached 15 to 25 years after the onset of diabetes. In type 2 diabetes, the appearance of proteinuria and the decline in GFR occur at a frequency similar to that seen in type 1 diabetes (3,7). In the child with prepubertal onset of diabetes, microvascular complications, including renal disease, tend to accelerate during puberty (8).

In addition to causing nephropathy, diabetes affects other components of the urinary system. Diabetes may predispose patients to urinary tract infection and papillary necrosis. Autonomic dysfunction can lead to bladder dysfunction with obstructive uropathy, which predisposes patients to urinary tract infection and, if obstruction is severe, often leads to loss of kidney function. Indeed, it is not uncommon for patients with type 2 diabetes to

**TABLE I.**

**CLINICAL STAGES OF DIABETIC NEPHROPATHY IN TYPE 1 DIABETES**

1. Renal enlargement and hyperfunction. RBF increased. GFR may be increased or within normal range. Evident at onset and persists for 5–15 years.
2. Microalbuminuria, the earliest evidence of incipient nephropathy, appears 10–15 years after onset of diabetes. GFR and BP are within normal range.
3. Macroalbuminuria evident after 1 to 5 years of microalbuminuria. GFR declining and BP elevated.
4. Progressive renal failure with severe macroalbuminuria and hypertension leading to ESRD 15–25 years after onset of diabetes.

BP = blood pressure; ESRD = end-stage renal disease; GFR = glomerular filtration rate; RBF = renal blood flow.

TABLE II.

## CHARACTERISTIC MORPHOLOGIC CHANGES IN THE DIABETIC KIDNEY

- Glomerular and tubular enlargement
- Thickening of glomerular and tubular basement membranes
- Expansion of mesangial matrix with diffuse and nodular glomerulosclerosis
- Formation of glomerular capsular drops and fibrin caps
- Arteriosclerosis and hyalinosis of afferent and efferent arterioles
- Tubulointerstitial fibrosis

have renal failure due to causes other than diabetic nephropathy. Renal artery stenosis due to accelerated atherosclerosis occurs more frequently in these patients than in the general population (9).

### MORPHOLOGIC CHANGES

The central pathologic change in the diabetic kidney is overproduction and impaired degradation of extracellular matrix components that lead to their accumulation in the basement membranes and mesangial regions of the glomerulus (**Table II**). The expanded mesangium results in a diffuse glomerulosclerosis and is sometimes accompanied by the formation of structures termed Kimmelstiel-

failure. The decline in GFR correlates better with the interstitial changes than with the glomerular changes (10,11).

### PATHOGENESIS OF DIABETIC RENAL HYPERTROPHY AND DISEASE

As stated, soon after the onset of diabetes, the kidneys hypertrophy and RBF and the GFR increase. This hyperfiltration is a consequence of renal vasodilatation, with greater dilatation of the afferent than the efferent glomerular arterioles (**Table III**). The result is an increase in the intraglomerular pressure, which drives more ultrafiltrate through the glomerular capillary wall (12). These hemodynamic changes contribute to the development of diabetic nephropathy by the effect of shear stress on the endothelial and mesangial cells, which respond by increasing growth factor, cytokine, and extracellular matrix production (13). The mechanisms for the altered intrarenal hemodynamics are not completely understood but appear to involve vasodilators such as nitrous oxide, prostanooids, and insulin-like growth factor-I. Systemic hypertension worsens the hemodynamic effects of diabetes on the kidneys and is an important, treatable mediator of progressive renal damage (14). Indeed, hypertension and diabetes are comorbid conditions that independently increase the risk of developing and accelerating both cardiovascular and renal disease (15).

Hypertension develops in 20% to 60% of diabetic patients, depending on age, ethnicity, and fat mass (14,15). In type 1 diabetes hypertension usually appears only after many years and develops in 12% to 25% of those with microalbuminuria; its

#### KEY POINT

**Systemic hypertension amplifies the risk of diabetic nephropathy. Hyperglycemia is key because of its direct effects on the cells and indirect effects via formation of metabolic derivatives and activation of signaling pathways.**

Wilson nodules (10,11). This process eventually leads to a reduction in the density of capillaries and in the glomerular filtration surface area. Permeability of the filtration barrier falls and, consequently, GFR declines. Extracellular matrix accumulates also in the tubular basement membranes and interstitial compartment. Progressive tubulointerstitial fibrosis also leads to nephron destruction and renal

TABLE III.

## PATHOGENIC FACTORS MEDIATING FUNCTIONAL AND STRUCTURAL CHANGES IN THE DIABETIC KIDNEY

- Altered renal hemodynamics
  - Vasodilatation
  - Increased blood flow
  - Glomerular hypertension and hyperfiltration
- Systemic hypertension
- Metabolic factors
  - Hyperglycemia with formation of glucotoxins, including circulating and local AGEs, and activation of signaling pathways, including the aldose reductase, PKC, and hexosamine pathways
  - Hyperlipidemia with vascular damage
- Increased production of renal growth factors and cytokines: AII, TGF- $\beta$ , CTGF, IGF-I, PDGF, eicosanoids, nitrous oxide
- Proteinuria
- Oxidative stress
- Genetic factors

AII = angiotensin II; AGEs = advanced glycation endproducts; CTGF = connective tissue growth factor; IGF-I = insulin-like growth factor-I; PDGF = platelet-derived growth factor; PKC = protein kinase C; TGF- $\beta$  = transforming growth factor- $\beta$ .

prevalence increases to 75% to 85% of patients with overt nephropathy (4). In type 2 diabetes hypertension is present in ~30% to 40% of newly diagnosed patients and its prevalence increases with time (5). Whereas in type 1 diabetes hypertension appears to be of renal origin, in type 2 diabetes hypertension is often present as part of the metabolic syndrome of insulin resistance where hyperinsulinemia may play an important role (15,16).

Key to the development of diabetic nephropathy is the hyperglycemic state, which has been postulated to mediate its effects in several different ways. First, glucose in sustained high concentrations may be directly toxic to cells, altering cell growth and gene and protein expression and increasing extracellular matrix and growth factor production (13). Second, glucose may induce its effects indirectly through the formation of metabolic derivatives such as oxidants and glycation products (17,18). Formation of advanced glycation endproducts (AGEs) may damage cells because of modifications to extracellular matrix proteins and to cellular proteins (19). The AGEs may also bind to cell-associated proteins that trigger abnormal cellular function.

Sustained production of certain glucose metabolites may result in the continuous activation of signaling pathways involving phospholipids and

kinases (17,18). The polyol pathway is one such pathway. Excessive entry of glucose into this pathway results in tissue accumulation of sorbitol, which leads to cataract formation and possibly osmotic vascular damage. Activation of this pathway may also alter various enzyme activities and thus contribute to the pathologic changes. Sustained hyperglycemia may also result in increased diacylglycerol levels with activation of protein kinase C. This kinase has been implicated as a cause of altered RBF, vascular permeability, and increased growth factor and extracellular matrix production in the diabetic kidney.

Several hormones, growth factors, and cytokines have been implicated in the pathogenesis of diabetic kidney disease (20,21). AII is a key mediator, and blockade of its generation or receptor binding has provided a major advance in the management of diabetic nephropathy (3,22,23). Apart from its hemodynamic actions, AII has several non-hemodynamic effects (22). These effects include the generation of reactive oxygen species, increased extracellular matrix accumulation, stimulation of transforming growth factor- $\beta$  (TGF- $\beta$ ), connective tissue growth factor, and platelet-derived growth factor production and macrophage activation (12,22). There is increasing evidence that TGF- $\beta$  is a major pro-sclerotic mediator. Its production is

stimulated by AII and by glucose directly. Preclinical studies have shown that TGF-β blockade prevents and also ameliorates diabetic nephropathy.

Recently it has been suggested that severe proteinuria, apart from being a marker of signifi-

**KEY POINT**

**Screening diabetic patients for microalbuminuria is crucial to slowing or preventing nephropathy—roughly 30% to 45% develop macroalbuminuria, which reflects the presence of established kidney disease. Microalbuminuria is an important predictor of not only renal disease but also cardiovascular disease.**

cant glomerular damage, may well serve to speed the progression of diabetic and other proteinuric kidney diseases (24). Studies in animals indicate that exposure of the tubular cells to high concentrations of filtered proteins and growth factors produces a tubulointerstitial inflammatory response that leads to progressive interstitial fibrosis. Correlative studies in humans lend further support to this idea. Thus, reducing proteinuria, such as that occurring with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers

(ARBs), may be of therapeutic value (3).

Since nephropathy develops in only 20% to 40% of diabetic patients, it is apparent that factors other than hyperglycemia are operative in the pathogenesis of kidney disease. Among these factors, genetics is important, as highlighted by the tendency of diabetic nephropathy to cluster in families and in ethnic groups such as the Pima Indian (25). Although the susceptibility genes have not been clearly delineated, genes encoding the angiotensin I converting enzyme, aldose reductase, and heparan sulfate may be involved.

**DIAGNOSIS AND MANAGEMENT OF DIABETIC NEPHROPATHY**

The onset of diabetic nephropathy is often silent, and because early intervention can slow its development and progression, it is important that diabetic patients be routinely screened for early evidence of renal involvement (2). A small increase in the amount of albumin excreted in the urine (microalbuminuria) is the earliest manifestation of nephropathy (Table IV) (4,26). Trace amounts of albumin are undetectable by dipstick; they must be measured by sensitive immunologic-based assays. The amount of albumin excreted is expressed relative to time or urinary creatinine level, which serves to correct for variations in urine concentration. Screening assays can be done on spot urine collections or timed collections over 24 hours or less. Because of the normal variability of albumin excre-

**TABLE IV.**

**MEASUREMENT AND SIGNIFICANCE OF URINE ALBUMIN EXCRETION**

Spot Collection µg/mg Creatinine	Urine Sample		Significance
	24-h Collection mg/24 h	Timed Collection µg/min	
<30	<30	<20	Normal
30–299	30–299	20–199	Microalbuminuria (incipient nephropathy)
≥300	≥300	≥200	Macroalbuminuria (clinical nephropathy)

Based on Mogensen CE, Schmitz O. The diabetic kidney: From hyperfiltration and macroalbuminuria to end-stage renal failure. *Med Clin North Am.* 1988;72:1465–1492. © 1988, with permission from Elsevier; Skyles JS. Microvascular complications. Retinopathy and nephropathy. *Endocrinol Metab Clin North Am.* 2001;30:833–856. © 2001, with permission from Elsevier; and Bakris GL. Microalbuminuria: What is it? Why is it important? What should be done about it? *J Clin Hypertens.* 2001;3:99–102. © 2001, with permission from Le Jacq Communications, Inc.

tion, assays should be repeated on 2 or 3 occasions over several months before the results can be considered indicative of renal involvement (**Table IV**) (2).

In patients with microalbuminuria, ~30% to 45% progress to macroalbuminuria over ~10 years, whereas a much smaller number regress to normoalbuminuria (27). Accordingly, when microalbuminuria is first detected, it is advisable to include a nephrologist in patient management. In addition to being predictive of the development of overt diabetic nephropathy, microalbuminuria represents a risk factor for the development of cardiovascular disease (16).

### Hypertension

Fortunately for the hypertensive diabetic patient, it is now well established that in addition to modifying the risk of cardiovascular disease and retinopathy, aggressive hypertension control can modify the natural history of diabetic kidney disease. Accordingly, careful measurement of blood pressure is important whenever the diabetic patient has an office visit. Several excellent studies (3,14,15,23) have established that antihypertensive therapy with a variety of agents can slow the progression of diabetic nephropathy.

Among the antihypertensive agents shown to be effective in lowering blood pressure in diabetic patients are diuretics,  $\beta$ -blockers,  $\alpha$ -blockers, calcium channel blockers, ACE inhibitors, and ARBs. Although there are only a few head-to-head comparisons of antihypertensive drugs, it is well documented that ACE inhibitors or ARBs can modify the progression of diabetic kidney disease, even in normotensive subjects. It appears these agents have a salutary effect beyond that obtained from lowering blood pressure.

In the landmark captopril study of type 1 diabetics (28), this ACE inhibitor significantly reduced the progression of diabetic nephropathy. Proteinuria decreased and the endpoints of doubling of the serum creatinine level, death, or ESRD were reduced by 50%. The effectiveness of ACE inhibitors in type 1 diabetes was subsequently confirmed in a meta-analysis of 12 clinical trials that showed ACE inhibitors reduced the risk of progression

from microalbuminuria to macroalbuminuria by 62% and that regression to normoalbuminuria was 3 times greater among treated patients than in control patients (29).

Three recent studies with the ARBs losartan and irbesartan in type 2 diabetic patients demonstrated the value of this class of agent (30–32). In microalbuminuric patients, irbesartan reduced the progression from microalbuminuria to macroalbuminuria. In patients with established nephropathy, the relative risk of time to the doubling of the serum creatinine and development of ESRD was reduced by irbesartan 33% and 37%, respectively, and by losartan 25% and 28%, respectively. Both losartan and irbesartan reduced overt proteinuria.

Because ACE inhibitors and ARBs have a salutary effect on the course of diabetic nephropathy over and above their blood pressure lowering effect, their usage forms the mainstay of hypertension control and renoprotection in diabetes. To date, there are no large-scale trials comparing the efficacy of ACE inhibitors with that of ARBs or studying the value of combination therapy. However, if hypertension or proteinuria persists with the use of a single agent, it has been suggested that these 2 agents be used in combination (33).

Antihypertensive treatment should be especially aggressive in the diabetic patient because of the high cardiovascular complication rate in these patients and the established benefit of lowering blood pressure (**Table V**). The recommended treatment goal is 130/80 mm Hg (15,34) or, in patients with proteinuria of >1g/day and impaired renal function, 125/75 mm Hg (34). The scheme for the use of antihypertensive agents needs to be adjusted on an individual basis, taking into account preexisting cardiovascular disease and the age of the patient. Initiation of therapy should include attention to lifestyle modifications, including weight loss, sodium restriction, moderate exercise, reduction of alcohol consumption, and smoking cessation. The latter is important since cigarette smoking has an adverse effect on the kidneys (35).

### Hyperglycemia

Two major clinical trials, the Diabetes Control and

## TABLE V.

## SCHEME FOR THE MANAGEMENT OF HYPERTENSION IN DIABETES

<b>Initial therapy</b>	<ul style="list-style-type: none"> <li>● Lifestyle modification, diet and exercise</li> <li>● ACE inhibitor/ARB with diuretic (monitor serum K and creatinine) Thiazide if creatinine &lt;1.8 mg/dL, loop diuretic if &gt;1.8 mg/dL</li> </ul>
<b>If goal not attained</b>	Add long-acting nondihydropyridine CCB
<b>If goal not attained</b>	Add $\beta$ -blocker if pulse >84 bpm or other subgroup of CCB if pulse <84 bpm
<b>If goal not attained</b>	Refer patient to hypertension specialist

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker. Goal: Blood pressure (BP) of 130/80 mm Hg, but if proteinuria >1 g/24 h and renal insufficiency present, then BP of 125/75 mm Hg. Based on Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis.* 2000;36:646–661. © 2000, with permission from Elsevier; and Molitch ME, DeFronzo RA, Franz MJ, et al. Diabetic nephropathy. *Diabetes Care.* 2003;26(Suppl 1):S94–S98. Reproduced with permission. Scheme should be adjusted according to individual circumstances, eg, coexisting cardiovascular or renal disease. Use of CCB and  $\beta$ -blockers should be modified in the elderly and patients with conduction defects. Use of ACE inhibitors and ARBs should be modified in patients at risk for hyperkalemia or with renovascular disease.

Complications Trial (DCCT) (36) and the United Kingdom Prospective Diabetes Study (UKPDS) (37), convincingly demonstrated that intensive glycemic control reduces the risk of developing microalbuminuria and nephropathy. Accordingly, the glycemic control recommendations provided by the American Diabetes Association should be rigorously followed.

### Dietary Protein Restriction

Although a clear benefit of dietary protein restriction has not been established, based on small positive clinical studies a protein intake of < 0.8 g/kg is recommended for patients with macroalbuminuria with further restriction when GFR falls.

### SPECIAL CONSIDERATIONS

When managing diabetic patients with impaired renal function it should be kept in mind that drug pharmacokinetics may change as renal function

declines. Thus, drug dosage may have to be modified. For example, insulin requirements may fall as kidney function declines, necessitating a reduction in dosage (38). In addition, metformin accumulates in renal failure and, as the risk of lactic acidosis increases, the drug should be discontinued. It is also important to recognize that patients with diabetic nephropathy are at increased risk for developing radiocontrast-induced renal failure (39); thus, radiocontrast-requiring procedures should only be carried out if essential. Azotemic patients should be well hydrated and low doses of contrast medium used.

It is also important to consider that renal failure in diabetic patients may arise for the same reasons it occurs in nondiabetic patients. For example, in the patient with autonomic neuropathy or in the older man who may have benign prostatic hypertrophy, an ultrasound to rule out obstructive uropathy is prudent. Also, since retinopathy eventually develops in virtually all patients with long-standing advanced diabetic nephropathy (14), the absence of retinopathy in a diabetic patient with overt renal disease raises the question whether a cause other than diabetes is responsible for the nephropathy.

Unfortunately, even with vigorous management and slowing of the course of the disease, established diabetic nephropathy is progressive, and when the advanced stage of renal failure is reached the criteria for transplantation or dialysis therapy for diabetic patients are the same as for nondiabetic

### KEY POINT

**Management of diabetic patients with nephropathy should include insulin and drug dosage changes (or suspensions) as renal function declines and early referral to a nephrologist.**

subjects. Early placement of a vascular access is especially important in diabetic patients because of problems caused by advanced atherosclerosis. It is generally believed that early initiation of dialysis may improve the clinical course.

## SUMMARY

Because of the frequent presence of comorbid conditions, the management of diabetic patients is more complex and the outcome worse than for non-diabetic patients. Thus, it is especially important in diabetic patients that renal involvement be detected early and that an intensive, multidisciplinary approach be applied to prevent the development and progression of renal disease and other complications of diabetes. In a recent study in which patients with type 2 diabetes and microalbuminuria were followed for an average of 8 years, it was shown that long-term, target-driven, intensified intervention aimed at multiple risk factors reduced the risk of cardiovascular and microvascular events—including nephropathy—by ~50% (40).

## REFERENCES

1. US Renal Data System. Excerpts from the United States Renal Data System 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. *Am J Kidney Dis.* 2001;38:S1–S248.
2. Molitch ME, DeFronzo RA, Franz MJ, et al. Diabetic nephropathy. *Diabetes Care.* 2003;26(Suppl 1):S94–S98.
3. Parving HH. Diabetic nephropathy: Prevention and treatment. *Kidney Int.* 2001;60:2041–2055.
4. Mogensen CE, Schmitz O. The diabetic kidney: From hyperfiltration and microalbuminuria to end-stage renal failure. *Med Clin North Am.* 1988;72:1465–1492.
5. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice. Nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2002;346:1145–1151.
6. Skyler JS. Microvascular complications. Retinopathy and nephropathy. *Endocrinol Metab Clin North Am.* 2001;30:833–856.
7. Ritz E, Tarnig DC. Renal disease in type 2 diabetes. *Nephrol Dial Transplant.* 2001;16(Suppl 5):11–18.
8. Lane PH. Diabetic kidney disease: Impact of puberty. *Am J Physiol Renal Physiol.* 2002;283:F589–F600.
9. Nicholls AJ. The impact of atherosclerotic renovascular disease on diabetic renal failure. *Diabet Med.* 2002;19:889–894.
10. Mauer M, Fioretto P. Diabetic nephropathy as a model for the use of renal structural endpoints in clinical trials. *Kidney Int Suppl.* 1997;63: S155–S158.
11. Dalla Vestra M, Saller A, Bortoloso E, et al. Structural involvement in type 1 and type 2 diabetic nephropathy. *Diabetes Metab.* 2000;26(Suppl 4): 8–14.
12. Brenner BM. Remission of renal disease: Recounting the challenge, acquiring the goal. *J Clin Invest.* 2002;110:1753–1758.
13. Raptis AE, Viberti G. Pathogenesis of diabetic nephropathy. *Exp Clin Endocrinol Diabetes.* 2001; 109(Suppl 2):S424–S437.
14. Jandeleit-Dahm K, Cooper ME. Hypertension and diabetes. *Curr Opin Nephrol Hypertens.* 2002;11: 221–228.
15. Arauz-Pacheco C, Parrott MA, Raskin P. Treatment of hypertension in adults with diabetes. *Diabetes Care.* 2003;26(Suppl 1):S80–S82.
16. Sowers JR. Update on the cardiometabolic syndrome. *Clin Cornerstone.* 2001;4:17–23.
17. Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA.* 2002;288:2579–2588.
18. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001;414: 813–820.
19. Vlassara H, Palace MR. Diabetes and advanced glycation endproducts. *J Intern Med.* 2002;251: 87–101.
20. Flyvbjerg A. Putative pathophysiological role of growth factors and cytokines in experimental diabetic kidney disease. *Diabetologia.* 2000;43: 1205–1223.
21. Rabkin R, Fervenza FC. Renal hypertrophy and kidney disease in diabetes. *Diabetes Metab Rev.* 1996;12:217–241.
22. Rincon-Choles H, Kasinath BS, Gorin Y, Abboud HE. Angiotensin II and growth factors in the pathogenesis of diabetic nephropathy. *Kidney Int Suppl.* 2002;82:8–11.
23. Hostetter TH. Prevention of end-stage renal disease due to type 2 diabetes. *N Engl J Med.* 2001;345: 910–912.
24. Ruggenenti P, Remuzzi G. The role of protein traffic in the progression of renal diseases. *Annu Rev Med.* 2000;51:315–327.
25. Rippin JD, Patel A, Bain SC. Genetics of diabetic nephropathy. *Best Pract Res Clin Endocrinol Metab.* 2001;15:345–358.
26. Bakris GL. Microalbuminuria: What is it? Why is it important? What should be done about it? *J Clin Hypertens (Greenwich).* 2001;3:99–102.
27. Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: Is albumin excretion rate sufficient? *Diabetes.* 2000; 49:1399–1408.
28. 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.
29. The ACE Inhibitors in Diabetic Nephropathy

- Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med.* 2001;134:370–379.
30. Parving HH, Hovind P. Microalbuminuria in type 1 and type 2 diabetes mellitus: Evidence with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers for treating early and preventing clinical nephropathy. *Curr Hypertens Rep.* 2002;4:387–393.
  31. 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.
  32. 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.
  33. Taal MW, Brenner BM. Combination ACEI and ARB therapy: Additional benefit in renoprotection? *Curr Opin Nephrol Hypertens.* 2002;11:377–381.
  34. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis.* 2000;36:646–661.
  35. Orth SR, Viedt C, Ritz E. Adverse effects of smoking in the renal patient. *Tohoku J Exp Med.* 2001;194:1–15.
  36. The 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.
  37. Turner RC. The U.K. Prospective Diabetes Study. A review. *Diabetes Care.* 1998;21(Suppl 3):C35–C38.
  38. Rabkin R, Simon NM, Steiner S, Colwell JA. Effect of renal disease on renal uptake and excretion of insulin in man. *N Engl J Med.* 1970;282:182–187.
  39. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: Incidence and risk factors. *Am J Roentgenol.* 1991;157:49–58.
  40. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med.* 2003;348:383–393.

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## Dialogue Box

### EDITORIAL BOARD

**Would you start an ACE inhibitor (ACEI) or an ARB in a diabetic patient with microalbuminuria even if the patient were normotensive?**

#### RABKIN

Yes, I definitely would. Once the presence of persistent microalbuminuria is confirmed on the basis of serial testing over time, I would initiate therapy with either an ACEI or an ARB. These agents reduce the progression and increase the regression from micro- to normoalbuminuria in both normotensive and hypertensive subjects. It is now well established that these agents also possess salutary actions independent of their blood pressure lowering actions.

### EDITORIAL BOARD

**On the basis of what yardstick would you titrate the dose?**

#### RABKIN

I would push the dose to the point where I eliminated the microalbuminuria, reached the maximal recommended dose, or was limited by the development of side effects. The more serious side effects include symptoms of hypotension, which is unusual in euvolemic subjects not receiving other antihypertensives; depressed renal function; and impaired potassium excretion with hyperkalemia.

### EDITORIAL BOARD

**In a patient with macroproteinuria that did not**

## Dialogue Box

**resolve despite a maximum dose of an ACEI, would you add an ARB?**

### **RABKIN**

Yes, I would. Although convincing data supporting such use are lacking, small-term studies suggest that dual blockade of the angiotensin system has an additive effect on reducing protein excretion and lowering blood pressure. Furthermore, a recent long-term study of patients with non-diabetic renal disease showed that dual therapy with an ACEI and ARB was more effective than either agent alone in reducing proteinuria and slowing the progression of the disease (Nakao N, Yoshimura A, Morita H, et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet*. 2003;361: 117–124). Thus, it would seem reasonable to use dual therapy in the diabetic in whom an optimal antiproteinuric effect (<1 gm protein/day) or blood pressure lowering effect has not been achieved.

### **EDITORIAL BOARD**

**Would you consider using this same combination in the patient with persistent microalbuminuria despite taking a maximum dose of an ACEI?**

### **RABKIN**

Although data supporting the use of dual therapy for microalbuminuria is limited, I would regard this as a reasonable approach in a patient with persistent microalbuminuria despite maximal ACEI dosage.

### **EDITORIAL BOARD**

**Would the use of a calcium channel blocker**

**(CCB) as opposed to an ARB in combination with an ACEI be just as effective?**

### **RABKIN**

The rationale for combining an ARB agent with an ACE inhibitor is that they act at different levels of the angiotensin system. ACE inhibitors do not produce complete inhibition of AII production; thus it is anticipated that in combination with an ARB, the adverse effects of angiotensin will be more completely abolished. Indeed as mentioned earlier, there is growing evidence that this combination has an additive salutary effect on proteinuria in diabetics and in nondiabetics, on the progression of kidney disease. It is noteworthy that this response is achieved in part through actions that are independent of blood pressure lowering effects. CCBs work by an entirely different mechanism and should not be regarded as a substitute for an ARB. While they are effective in lowering blood pressure and can reduce proteinuria, there are currently no studies indicating that they are effective in slowing the progression of diabetic nephropathy. CCBs are very useful as additional therapy when inhibition of the angiotensin system fails to provide optimal blood pressure control.

### **EDITORIAL BOARD**

**Pushing the envelope even further, would you favor starting an ACEI or ARB in the diabetic patient in a preemptive fashion even prior to the development of microalbuminuria?**

### **RABKIN**

That would not be my recommendation. However, my threshold for starting such an agent would be fairly low in a diabetic patient who had another indication for its use such as hypertension or left ventricular dysfunction.

## Dialogue Box

### EDITORIAL BOARD

**When should the diabetic patient with nephropathy be referred for placement of a vascular access for future dialysis?**

### RABKIN

The involvement of a nephrologist should generally be sought once microalbuminuria develops and certainly when the serum creatinine begins to rise. Having said that, one should consider the placement of a vascular access and referral for consideration for renal transplantation, when the GFR drops below 25 mL per minute. (The GFR can

easily be estimated from the serum creatinine level with the GFR calculator at the Web site of the National Kidney Foundation <http://www.kidney.org/professionals/doqi/palm.cfm>). Ideally a vascular access should be placed within 1 year of the anticipated need for dialysis, which is indicated when the GFR falls below 15 mL/min but varies according to the clinical status of the individual patient.

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