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CME CREDIT HOURS

Diabetic nephropathy: strategies for preventing renal failure

KEY POINTS:

Diabetic nephropathy progresses in a continuum of five stages from normal renal function through stages of proteinuria and ultimately renal failure.

Testing for microalbuminuria can identify patients at risk.

Rigorous glycemic control can reduce the incidence of microalbuminuria and also slow the progression from microalbuminuria to macroalbuminuria.

Aggressive antihypertensive treatment, especially with angiotensin-converting enzyme inhibitors, slows the progression of diabetic nephropathy, even when renal function has declined. Data suggest the goal blood pressure should be less than 135/85 mm Hg — lower than to prevent other complications of high blood pressure.

A low-protein diet may also slow diabetic nephropathy, but this has not been conclusively proved.

ABSTRACT: Better understanding of diabetic nephropathy's pathophysiology has led to fundamental changes in its management: detecting nephropathy early and intervening with rigorous glycemic control and aggressive management of hypertension may slow its progression. Dietary protein restriction may also have a role.

Diabetic nephropathy is a common and potentially debilitating complication of diabetes mellitus, and all physicians who care for diabetic patients should take measures to detect, prevent, or treat it.

THE MAGNITUDE OF THE PROBLEM

Diabetic nephropathy is common and, often occurring in people who would otherwise be in the prime of life, imposes a substantial burden in diminished quality of life, cost of care, lost wages, and mortality.

Approximately 35% of patients with type I or insulin-dependent diabetes mellitus (IDDM) eventually develop nephropathy.[1] Although a much lower percentage of persons with type II or non-insulin-dependent diabetes mellitus (NIDDM) develop end-stage renal disease than with type I diabetes, type II is much more common and is a leading cause of renal failure.

Together, both types of diabetes are the cause of renal failure in half of all dialysis patients.[2,3] A greater percentage of African-Americans, Asians, American Indians, and Mexicans with diabetes suffer end-stage renal disease than do whites.[4]

Diabetic nephropathy is a leading cause of death in type I diabetes, accounting for approximately 60% of deaths in some series.[1,5,6]

TABLE

CLINICAL PROGRESSION, DIAGNOSIS, AND MANAGEMENT OF DIABETIC NEPHROPATHY

Stage	Clinical features	Blood pressure	Glomerular filtration rate	Protein excretion	Frequency of testing		
					$HgbA_{1C}$*	24-hour albumin excretion	24-hour creatinine clearance
1	Hyperfiltration	Normal	Normal or increased	None (< 30 mg/24 h)	Every 3–6 months	At baseline (type II) Or after 5 years (type I) Then every 6–12 months	
2	Hyperfiltration with histologic changes	Normal	Normal or increased	None	Every 3–6 months	Every 6–12 months	
3	Incipient nephropathy	Normal or high	Normal, increased, or decreased	Microalbuminuria (30–300 mg/24 h)	Every 3–6 months	Every 6–12 months	Every 6–12 months
4	Overt clinical nephropathy	Usually high	Normal or decreased	Macroalbuminuria (> 300 mg/24 h)	Every 3–6 months	Every 6–12 months	Every 6–12 months
5	End-stage renal disease	High	Decreased	Macroalbuminuria	Every 3–6 months	Determined by clinical circumstances (eg, nephrotic syndrome)	Every 3–12 months‡

* Glycated hemoglobin; to assess glycemic control † Angiotensin-converting enzyme ‡ Not necessary on dialysis

HOW KIDNEY FUNCTION IS LOST

Although the progression of diabetic nephropathy to end-stage renal disease varies among patients and its evolution is a continuum,[7] diabetic nephropathy has five definable stages (**TABLE and FIGURE**).

Stage 1: Hyperfiltration

Early in the course of type I diabetes, the glomerular filtration rate may increase to well above normal.[8]

This stage has been studied less in type II diabetes, but in studies reviewed by Alzaid,[9] the prevalence of microalbuminuria (which occurs in later stages, see below) ranged from 20% to 40%. The duration of stage 1 varies, lasting up to 15 years.

What causes hyperfiltration is not completely understood; however, glomerular filtration increases with even mild hyperglycemia,[10] and improved glycemic control leads to a marked reduction in hyperfiltration.[10,11] Usually absent in this stage are albuminuria and, presumably, any histologic changes of diabetes mellitus in the kidneys.

Stage 2: Hyperfiltration with histologic changes

Stage 2 is clinically indistinguishable from stage 1, but biopsy reveals histologic changes of diabetes mellitus in the kidney.

Intermittent microalbuminuria may occur

during episodes of hyperglycemia (perhaps because of increased glomerular filtration) or exercise. It is not yet clear whether intermittent microalbuminuria under these conditions always leads to diabetic nephropathy.

Serum creatinine and potassium	Treatment options
	Rigorous glycemic control
	Rigorous glycemic control
Every 3–6 months	Rigorous glycemic control Aggressive antihypertensive treatment (ACE† inhibitors preferred) ACE inhibitors in normotensive patients (not proved) Protein restriction (not proved)
Every 3–12 months	Rigorous glycemic control Aggressive antihypertensive treatment (ACE inhibitors preferred) ACE inhibitors in normotensive patients Protein restriction (not proved)
Every 3–12 months	Aggressive antihypertensive treatment Protein restriction Potassium restriction Calcium and vitamin D supplements Dialysis or transplantation

Stage 3: Incipient nephropathy

Stage 3 is marked by persistent microalbuminuria — urinary albumin excretion of 30 to 300 mg/24 hours (20 to 200 µg/minute).[9,12,13] This rate is higher than normal but not detectable by usual "dipstick" urine tests, which can detect protein only at concentrations greater than 300 mg/24 hours.

Effects of microalbuminuria. Microalbuminuria has several important, well-documented consequences. It can progress to clinical nephropathy[13] and is a risk factor for cardiovascular disease and cardiovascular mortality[14,15] (perhaps because of the increased frequency of hypertension in patients with microalbuminuria or because of increased genetic susceptibility to hypertension or other cardiovascular risk factors). It is also a risk factor for proliferative retinopathy and cardiomyopathy.[17]

Why microalbuminuria develops in some patients with type I diabetes and not in others is a subject of investigation. Genetic susceptibility may be one explanation. There is concordance of proteinuria and risk for end-stage renal disease when there are two or more siblings with type I diabetes in the same family.[16]

Parents of persons with diabetes and proteinuria have higher arterial blood pressures than do parents of persons with diabetes but no proteinuria,[17] and groups with a high prevalence of hypertension also have a high prevalence of diabetic nephropathy. These observations support the concept that a genetic susceptibility to nephropathy and hypertension may be linked.

Stage 4: Clinically overt nephropathy

Proteinuria increases as diabetic nephropathy progresses; after 5 to 10 years of persistent microalbuminuria, the urine becomes persistently positive for albumin with a dipstick test. This stage inexorably progresses to end-stage renal disease. Hypertension is common, and the higher the blood pressure, the faster the loss of renal function. In contrast, age and sex seem to have no effect on the rate of loss of renal function.

During this stage, clinicians must rule out nondiabetic causes of worsening renal function. Signs that worsening of renal function is not caused by diabetic nephropathy include rapid decline in glomerular filtration rate in a patient who previously had a glomerular filtration rate close to normal, proteinuria in a patient who has had diabetes less than 5 to 10 years, sudden onset of the nephrotic syndrome (ie, massive proteinuria), hematuria, and absence of retinopathy. A diagnostic renal biopsy may be necessary under these circumstances.

Intrarenal hypertension is thought to cause renal damage in many diseases,[18] including diabetic nephropathy. Extracellular volume expansion leads to dilation of the arterioles in the kidney, allowing systemic pressures to reach the glomerular capillaries and causing adaptive hyperfiltration, hypertrophy,[19] capillary damage, and progressive loss of glomeruli. As more glomeruli are lost, further hyperfiltration becomes necessary, and the damage intensifies.

Stage 5: End-stage renal disease

In stage 5, renal function progressively declines, ultimately leading to end-stage renal disease and the need for dialysis or transplantation. Patients with end-stage renal disease of any cause may have hyperkalemia, uremic symptoms, and abnormalities of calcium, phosphorus, vitamin D, and parathyroid hormone.

In general, management of this stage is similar to that for nondiabetic end-stage renal disease, and the indications for dialysis and transplantation are the same. Because specialists rather than primary-care physicians usually undertake the care of such patients, we will not discuss it in detail here.

■ DETECTING DIABETIC NEPHROPATHY

In type I diabetes

The American Diabetes Association[20,21] recommends annual testing for microalbuminuria starting 5 years after type I diabetes has been diagnosed, and the National Kidney Foundation and the European IDDM Policy Group have similar guidelines.[22,23]

Screening should begin with a dipstick test for macroalbuminuria. Patients without macroalbuminuria should then have a test for microalbuminuria with a timed (12- or 24-hour) or "spot" (corrected with creatinine) urine collection. Normal urinary protein in spot collections is <30 mg of protein/g creatinine; microalbumninuria is between 30 and 300 mg of protein/g creatinine, and macroalbuminuria is >300 mg of protein.

How often to test has not been established by clinical studies, but testing once or twice a year in hypertensive diabetic patients can be justified on the basis of the natural history of the disease. The optimal frequency in normotensive patients and the advantages of timed vs spot urine collections remain to be determined.[24] Current guidelines [21,22] recommend annual testing of normotensive patients.

Because albumin excretion is a risk factor for cardiovascular events and death, physicians should also increase their vigilance in detecting and treating other cardiovascular risk factors in patients with nephropathy.

In type II diabetes

Patients with type II diabetes should have a test for microalbuminuria at the time of diagnosis, because many patients present several years after the onset of disease. Although proteinuria in type II diabetes is not always due to diabetes,[9] management strategies assume such a relationship. Follow-up testing is similar to that in type I diabetes mellitus.

In overt diabetic nephropathy

In patients with clinically evident diabetic nephropathy (dipstick-positive albuminuria or increased serum creatinine concentration), a 24-hour urine sample should be collected for a quantitative protein determination and creatinine clearance. This will help confirm the diagnosis of diabetic nephropathy and provide a baseline by which to monitor therapy.

Creatinine concentrations should then be measured at least annually; an increase may justify a repeat 24-hour measurement of protein excretion and creatinine clearance and a workup for other causes of renal failure, especially if the increase is large or rapid.

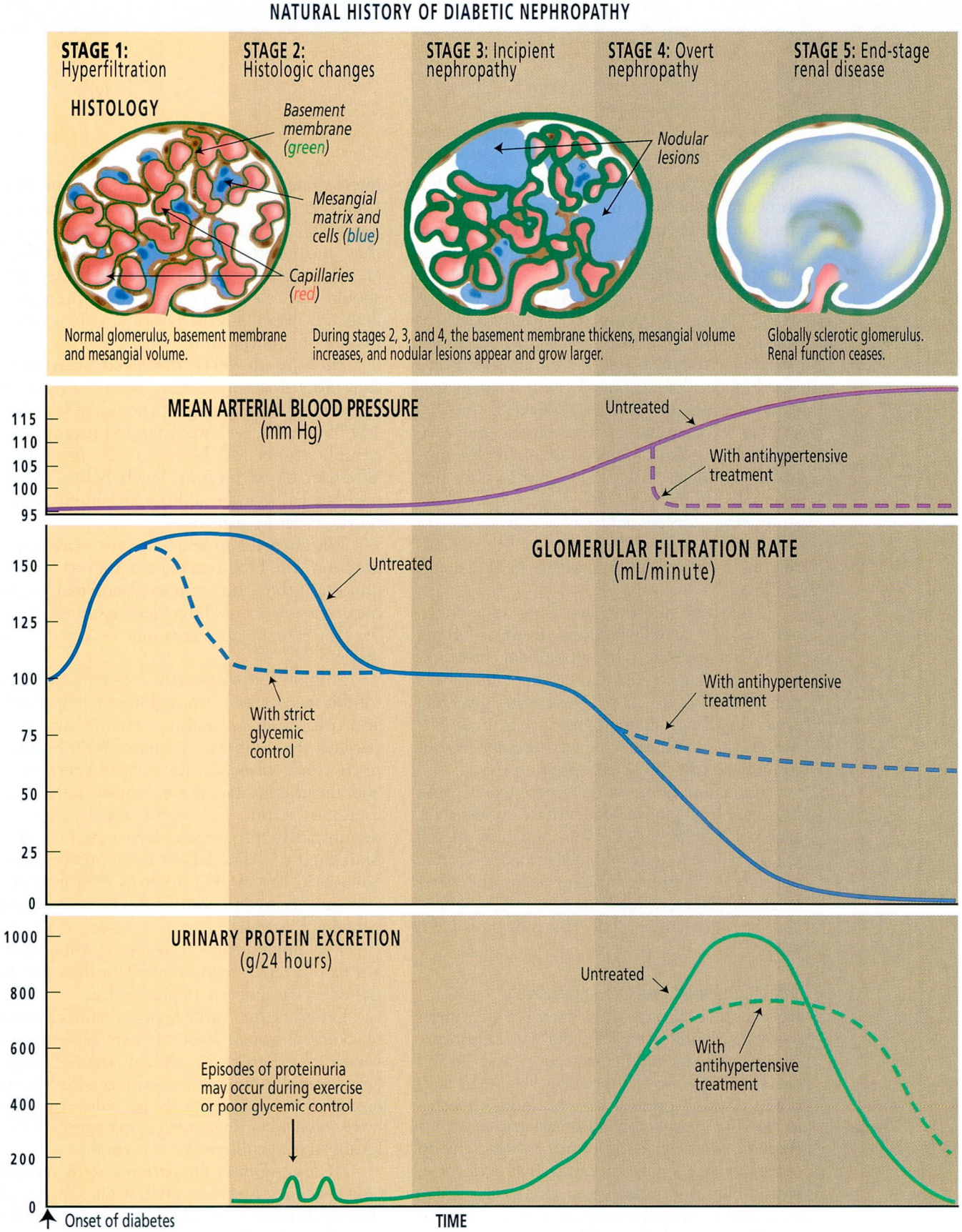
For example, if a serum creatinine that has been in the normal range doubles in a year, this indicates a 50% loss of renal function. Such a rapid rate of decline is unusual in diabetic nephropathy and necessitates an evaluation for other causes of declining renal function.

■ STRATEGIES FOR PREVENTING RENAL FAILURE

Three strategies to prevent diabetic nephropathy from progressing to renal failure should be considered: rigorous glycemic control, aggressive treatment of hypertension, and low-protein diets. Although how these interventions prevent renal failure remains to be determined, all seem to reduce protein excretion — and some evidence suggests that proteinuria itself may be toxic to the kidney.[25,26]

Control blood sugar levels rigorously

Histologic studies in animals and short-term studies of proteinuria in humans have suggested that glycemic control reduces the risk of



Normal progression of blood pressure, glomerular filtration rate, and proteinuria through the stages of diabetic nephropathy. Dotted lines indicate the effect of different therapeutic interventions on these variables.

diabetic nephropathy.[27] The human studies showed reduction in hyperfiltration and microalbuminuria, but did not demonstrate a clear effect on the rate of progression of overt diabetic nephropathy.

The Diabetes Control and Complications Trial,[28–31] the best prospective study to date to address this question, randomly assigned patients with type I diabetes to undergo intensive blood glucose control (with a target glycated hemoglobin [$HgbA_{1C}$] level of 6.05%) or standard treatment. Intensive glycemic control reduced the incidence of microalbuminuria by about 50%. In patients who had microalbuminuria at the beginning of the study, strict control led to a lower incidence of macroalbuminuria. We assume that these findings also apply to patients with type II diabetes mellitus.

The trial did not last long enough to demonstrate a delay in progression of renal failure as measured by glomerular filtration rate. It is not clear whether there may be a point beyond which even rigorous glycemic control will not slow progression of renal failure, and no large studies have been carried out in humans to address this question.

Recommendations. It is best to keep the average blood glucose concentration less than 150 mg/dL ($HgbA_{1C}$ < 7.0%) and close to 120 mg/dL ($HgbA_{1C}$ 6.0%). Rigorous glycemic control is clearly advantageous in the early stages of diabetes. We believe it is also beneficial in later stages, but this has not been proved.

Treat high blood pressure aggressively

In several studies, antihypertensive treatment in patients with established diabetic nephropathy decreased albumin excretion and slowed deterioration of renal function.[26,32–36] In fact, blood pressure control may be more effective in slowing progression (and easier to achieve) than rigorous glycemic control, especially in more advanced stages of renal dysfunction (ie, with albuminuria, decreased glomerular filtration, and increased creatinine concentration).

Recommendations. The data are less clear in earlier stages, because whether a decrease in microalbuminuria delays or prevents progression to end-stage renal disease still needs to be answered conclusively. However, we believe that antihypertensive treatment is beneficial at all stages of diabetic nephropathy and should start soon after high blood pressure is detected, especially in persons with a family history of hypertension.

How far to lower the blood pressure to slow progression of diabetic nephropathy is not known, but data suggest it should be less than 135/85 mm Hg — lower than to prevent other complications of high blood pressure.[33] Whether blood pressure levels below 135/85 mm Hg will confer additional benefit is currently under investigation.

Which drug to use? In protecting renal function, the blood pressure achieved is more important than the agent used, and many antihypertensive agents have demonstrated benefit. However, some agents may be better than others.

Angiotensin-converting enzyme (ACE) inhibitors decrease intraglomerular pressure and proteinuria, making them attractive choices in diabetic patients.[30,36] Sodium restriction enhances their antihypertensive and antiproteinuric effects. However, they can increase serum potassium levels, and as nephropathy progresses, hyperkalemia may limit their use. The largest randomized studies have used the ACE inhibitors captopril and enalapril, but other ACE inhibitors are likely beneficial as well.

The angiotensin II receptor antagonists are also currently being studied for their potential effect on diabetic nephropathy.

Less data are available on calcium channel blockers, although some of them have shown benefit.[37] Whether all calcium channel blockers confer the same effect on protecting renal function is not yet resolved. Diltiazem may have some advantages over other agents. Only future studies will resolve this issue.

ACE inhibitors for patients with normal blood pressure? Several small studies suggested that ACE inhibitors reduce albumin excretion and slow the decline in renal function in patients with diabetes and albuminuria but

normal blood pressure.[38,39] Since albuminuria predicts the risk for nephropathy, and the course of renal function loss is usually predictable, one might assume that such therapy may slow the progression to end-stage renal disease. Further studies in this area will likely prove this true. However, use of ACE inhibitors in normotensive diabetic patients should not yet be considered standard therapy. A common practice is to start treatment with a low dose of an ACE inhibitor, pending the results of ongoing trials.

Limit protein intake — probably

Although low-protein diets reduced hyperfiltration and microalbuminuria and slowed progression of overt nephropathy in animal studies,[40,41] there is much less evidence of such benefit in humans.[42-44]

Patients with diabetes were generally excluded from the best study to date of low-protein diets in renal disease, the Modification of Diet in Renal Disease (MDRD) study, although a few patients with type II diabetes were enrolled. Preliminary results from this study did not show protein restriction beneficial in slowing the decline of renal function, perhaps because of limited benefit in patients with polycystic kidney disease.[29,45]

Henry,[46] reviewing the available studies, concluded that it has not been determined at what stage of diabetic nephropathy to institute dietary protein restriction, nor is it clear what is the optimal level of protein restriction.

Even if protein restriction proves beneficial, patients may not comply in the long term. Further, although no obvious ill effects of low-protein diets in patients with diabetic nephropathy have been found, the issue of safety (including malnutrition) with long-term use is still a concern.

Recommendations. A diet containing 0.8 g of protein per kg of body weight is recommended for all patients with diabetes. This amount, which is the recommended dietary allowance for all adults, is much less than most persons consume. Diets containing less protein (0.6 g/kg/day) generally are difficult for patients to follow for long.[24,46-48]

For patients with more advanced nephropathy and uremic symptoms, protein restriction is a viable option, as it may reduce uremic symptoms. If the physician feels that a low-protein diet is realistic, he or she should refer the patient to a dietitian to implement it.

Lower lipid levels — maybe

Tantalizing data suggest that lowering lipid levels (or some property of lipid-lowering drugs not related to their effect on lipids) may slow diabetic nephropathy. However, the data are preliminary and do not yet justify lipid-lowering treatment, except according to established guidelines to prevent atherosclerotic disease. ■

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