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Diabetic Nephropathy for the Primary Care Provider: New Understandings on Early Detection and Treatment

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ABSTRACT

Background: Diabetic nephropathy is the leading cause of renal disease in the United States, occurring in 20%-40% of patients with diabetes. This condition is a distinct manifestation of diabetic renal disease seen in patients with type 1 and type 2 diabetes. Despite clear screening and management recommendations, diabetic nephropathy remains substantially underdiagnosed.

Methods: This review presents recent guidelines and recommendations from varied work groups to identify, monitor, and halt the progression of diabetic nephropathy. Our search of the recent literature focused on diagnostic criteria, the latest screening recommendations, novel screening methods, current research, new treatment recommendations, and goals for early intervention.

Results: Current recommendations for early detection and treatment of diabetic nephropathy include yearly albumin to creatinine ratio checks and more frequent tests if indicated based on glomerular filtration rate and albuminuria; optimizing glucose control with a target hemoglobin A1c goal of $<7\%$; initiating angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as the first line in disease management with dual therapy of ACE inhibitors and ARBs no longer recommended; managing blood pressure with a goal of $<140/90$ mmHg as the target for all patients with diabetes; and initiating statin therapy for patients <50 years old and with concomitant chronic kidney disease and diabetes and in all patients with chronic kidney disease >50 years of age regardless of the coexistence of diabetes.

Conclusion: With early detection, proper screening, and management, the impact of diabetic nephropathy may be better mitigated to lessen its impact on society and healthcare.

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INTRODUCTION

The total number of patients with diabetes has steadily increased in most countries, including the United States, in the past few years.[1] Diabetes has been described as a catalyst for a number of conditions, most notably cardiovascular disease, retinal disease, and renal disease.[1-4] Diabetic nephropathy (DN) is a distinct manifestation of diabetic renal disease that is seen in patients with both type 1 and type 2 diabetes mellitus (DM).[2] DN has been recognized as the leading cause of renal disease in the United States, occurring in 20%-40% of patients with DM, and despite clear screening recommendations, remains substantially underdiagnosed.[1,5,6] This article highlights recent research and guidelines regarding DN screening modalities, advances in management, and early prevention strategies.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Data from de Boer et al illustrated that the prevalence of DM in the United States increased from 7.4% to 9.6% from 1988 to 2006, and this trend is forecast to continue.[6] This escalation has resulted in a concomitant, proportional increase in end-stage renal disease (ESRD).[6,7] The work of de Boer et al showed that DN accounts for 44% of new ESRD cases with 6% attributed to type 1 DM, 38% attributed to type 2 DM, and a projected increase of 3 million cases over the

Table 1. Albuminuria Categories in Chronic Kidney Disease

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased[a]
A3	>300	>30	>300	Severely increased[b]

AER, albumin excretion rate; ACR, albumin to creatinine ratio.
[a]Relative to young adult level.
[b]Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).
(Reprinted with permission from *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*.[11])

course of 20 years.[6] The prevalence of DN is more notable among African Americans, Asians, and Native Americans than it is among Caucasians. Risk factors for DN include poor glycemic control, hypertension, tobacco use, and age of onset.[3-5,7,8]

Recent literature increasingly has attempted to map the pathophysiology and progression of renal disease in the setting of DN. DN is a chronic disease state that is manifested by glomerular hypertrophy, transient hyperfiltration, proteinuria, renal fibrosis, and ultimately a decrease in glomerular filtration rate (GFR).[2,3,8,9] Hyperglycemia appears to be the driving force in the progressive destruction of the glomeruli. Chronically elevated blood glucose leads to the formation of advanced glycosylated products with subsequent hyperfiltration (a potential increase of 5%-10% in GFR) and glomerular hypertrophy.[1] Additionally, mechanical strain and shear stress occurring in tandem, as a result of the altered hemodynamics of the glomeruli, lead to the release of numerous cytokines, proinflammatory markers, and growth factors that stimulate several oxidative stress pathways.[2,7-9] The results are the development of albuminuria; decline in GFR and the release of vasoactive and inflammatory cytokines; and progressive interstitial fibrosis and tubular atrophy.[1]

DIAGNOSTIC FEATURES

One of the earliest characteristic changes caused by DN, prior to any alteration in serum creatinine, is the appearance of protein in the urine.[7,8,10] Albumin has become the recommended protein screening modality because of its manifestation in the majority of chronic kidney disease (CKD) cases, its sensitivity to glomerular permeability, and the standardization of assays.[11] With current assays, large fluctuations in albumin excretion can be detected without a significant increase in total urinary protein.[11] Albuminuria is defined as pathologic albumin excretion into the urine secondary to the changes that occur in the glomerulus from the mechanisms described previously.[1-3,7,8,10-12] The current gold standard diagnostic test for DN is the amount of albuminuria seen on 24-hour urine collection. A more common and convenient estimation consists of the spot albumin to creatinine ratio (ACR) that can be performed in an office setting and is often used as a surrogate to the 24-hour collection.[1-3,5,7,8,10,11] The rate of albumin excretion corresponds to 1 of 3 albuminuria stages: A1, A2, or A3 (Table 1).

Normal (Stage A1) and Moderately Increased Albuminuria (Stage A2)

In the past, urine dipsticks were only able to quantify albuminuria above 300 mg/d, but with newer assays, smaller quantities can now be measured. In healthy individuals, the acceptable rate of albumin excretion in the urine is <30 mg/d.[1,2,5,7,11] Results <30 mg/d correspond to stage A1 albuminuria.

The range of albuminuria from 30 mg/d to 300 mg/d was once labeled microalbuminuria. Liberal use of this term has come under scrutiny, and common practice now recommends classifying individuals with microalbuminuria as having moderately increased albumin urinary excretion (stage A2).[11] According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), the lower variant of stage A2 albuminuria is defined by an albumin excretion rate of 20 mcg/min, which is equivalent to 30 mg/d, and to an ACR of 30 mg/g. The upper variant is defined as 200 mcg/min, which is equivalent to 300 mg/d, and to an ACR of 300 mg/g.[1,2,7,8,10,11] Given these definitions, stage A2 is characterized by albuminuria between the range of 30 mg to 300 mg per 24-hour collection or ACR.[1,2,7,8,10-12]

Severely Increased Albuminuria (Stage A3)

If albuminuria advances beyond 300 mg/d or 300 mg/g as determined by ACR, it is categorized as stage A3, representing severely increased albumin urinary excretion (formerly known as macroalbuminuria).[7,8,10-12] Stage A2 is estimated to progress to stage A3 at a rate of 2%-3% per year and is associated

with a decrease in GFR.[7,8] This statistic should serve as a warning for clinicians that DN can be a relatively quickly progressing disease, and diligent workup and monitoring are essential to delay progression.[7]

Although stage A2 is considered a risk factor for progression to stage A3, not all patients progress, and some even regress to stage A1 (near-normal levels).[11,12]

The KDOQI group notes that patients with type 1 and type 2 DM have considerable variability in albuminuria, and the degree of albumin in the urine may not reflect true underlying kidney disease,[7] as hypertension may contribute to proteinuria even in patients without a diagnosis of DM.[7,8,12] Albuminuria is an established risk factor for progressive cardiovascular disease, even at the lower detectable levels.[1] An ACR increase of 3.5 mg/g has been reported to increase the risk of a cardiovascular event (ie, myocardial infarction or stroke) by 5.9%.[1]

SCREENING

Gross et al pointed out that studies from the 1980s showed a progression rate from stage A2 to stage A3 in up to 80% of patients with type 1 DM over a 14-year period, while later studies show a progression rate of 30%-45% over a 10-year period.[5] The reduced progression rate may be the result of an increased awareness of DN and regulation of hyperglycemia and hypertension in recent years.[5] Although the reduced progression rate represents a substantial improvement in the management of DN, greater effort still is necessary in screening and early therapeutic intervention.

As previously discussed, stage A2 is an early marker for DN and is useful as a screening tool for early diagnosis and treatment.[7,8,10-12] A few relatively inexpensive tests are available for the diagnosis of moderately increased albuminuria. The 24-hour urine collection is widely considered the gold standard diagnostic test; however, the collection process is cumbersome and errors may occur.[5,7,8,10-12] According to KDOQI and the American Diabetes Association (ADA), the ACR is currently the recommended first-choice test, especially when completed with the first morning void.[7,10,11] Studies have shown sensitivity and specificity as high as 85% when compared to other-timed voids.[7] As with every screening test, the results have limitations, and urinary albumin excretion can be variable. Thus, current guidelines recommend that every abnormal ACR test should be confirmed by 2 additional samples collected over the course of 3-6 months. A positive stage A2 screen is defined as 2 of 3 abnormal ACR tests.[7,8,10,12] Additionally, screening should not be performed in conjunction with conditions that may increase the urinary excretion of albumin, such as urinary tract infections, hematuria, trauma, febrile illnesses, uncontrolled hypertension, pronounced hyperglycemia, and vigorous exercise.[5,7,10,12]

Because of variations in the pathologic process of DN, initial screening recommendations for patients with type 1 and type 2 DM differ. The nature of type 2 DM is more indolent compared to type 1 DM, and significant renal damage may have already occurred by the time of diagnosis, with up to 7% of this patient population already having developed albuminuria.[5] Screening for stage A2 albuminuria is therefore recommended for all patients with type 2 DM at the time of diagnosis.[5,7,8,10-12] Patients with type 1 DM, on the other hand, will be diagnosed before renal damage has a chance to occur; therefore, screening can be delayed until 5 years after diagnosis.[5,7,8,10-12] Some studies estimate that up to 18% of patients with type 1 DM may have proteinuria present before the 5-year screening milestone.[5] Clinicians therefore can reasonably begin screening for DN in selected patients before the 5-year mark, such as those with poor glycemic control, noncompliance with therapy, poor lipid control, and poor blood pressure control.[5,7,8]

Although albuminuria is widely accepted as the primary marker for diabetic renal disease, recent studies have suggested that patients with DM may begin to show signs of renal disease prior to an albuminuria diagnosis.[13] Caramori et al looked at 105 patients with type 1 DM without signs of albuminuria and found that 23 had already developed advanced renal disease. This finding suggests that decreasing GFR in long-standing stage A1 patients may be a marker of disease progression.[12,13] Additionally, patients with type 2 DM were found to progress to significant renal damage while still having normal albuminuric levels.[14] These findings suggest that even though albuminuria is an important finding and a marker of disease, the lack of albumin does not necessarily signify a disease-free state and other markers, such as GFR, need to be used in tandem to screen for the progression of disease.[11,14]

GFR is one of the most used markers for CKD diagnosis and monitoring and should be calculated for all patients with DM.[1,5] GFR is most commonly estimated via the Modification of Diet in Renal Disease (MDRD) study equation. By convention, stages of CKD have been divided into 5 groups based on GFR: G1 is a GFR $>$90 mL/min/1.73 m^2; G2 is 60-89 mL/min/1.73 m^2; stage G3 has been divided into G3a and G3b ranging from 45-59 mL/min/1.73 m^2 and 30-44 mL/min/1.73 m^2, respectively; G4 is 15-29 mL/min/1.73 m^2; and G5 (also known as ESRD) is $<$15 mL/min/1.73 m^2. Measurements tend to be the most accurate for CKD stage G3 and below.[7,15] The

Table 2. Screening Recommendations Based on Glomerular Filtration Rate and Albuminuria in Diabetic Nephropathy

Glomerular Filtration Rate Stage	Filtration Rate, mL/min/1.73 m^2	Frequency of Screening Based on Albuminuria			
		Annual	Biannual	4 Months	Close Monitoring[a]
G1	>90	A1,[b] A2[c]	A3[d]		
G2	60-89	A1, A2	A3		
G3a	45-59	A1	A2	A3	
G3b	30-44		A1	A2, A3	
G4	15-29			A1, A2	A3
G5	<15				A1, A2, A3

[a]Every 1-3 months.
[b]Albuminuria stage 1, <30 mg/g.
[c]Albuminuria stage 2, >30 mg/g to <300 mg/g.
[d]Albuminuria stage 3, >300 mg/g.
Note: Data extrapolated from KDIGO 2012 Evaluation and Management of chronic kidney disease.[11]

equation uses the clearance of endogenous creatinine and attempts to estimate the GFR based on age, sex, and race.[5,15] Many applications are now freely available for both iOS and Android systems that will quickly calculate GFR for the clinician using the MDRD-based equation. The equation is as follows:

$$\text{GFR} = 186 \times \Big[\text{serum creatinine}\,(\text{mg/dL})^{-1.154} \times \text{age}\,(\text{years})^{-0.203} \times 0.742\,(\text{if female}) \times 1.210\,(\text{if African American})\Big]$$

GFR and albuminuria may be largely independent of each other, and a sole GFR or albumin measurement is insufficient to fully appreciate the current disease state of DN. With recent studies suggesting that decreased GFR and increased albuminuria are associated with amplified disease progression, frequent measurements and assessments of both GFR and albuminuria should be undertaken.[11] Regular monitoring in selected patients with elevated levels is imperative to tailor management appropriately.[11] Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines encourage clinicians to monitor both GFR and albumin annually—more frequently in selected patients—to consider the risk of disease progression and therapeutic management (Table 2).[11] Nephrology consultation is also recommended once the GFR falls below 30 mL/min/1.73 m^2 for potential initiation of renal replacement therapy.[5,7,10-12]

Cystatin C–Based Equations

Although widely endorsed as a screening tool for DN, the MDRD equation has limitations.[1,16] The MDRD has been reported to underestimate the rate of decline in kidney function and to underestimate filtration rate, especially in patients with near-normal renal function, by 9%-29%.[15,16] Additionally, head-to-head studies between the MDRD equation and the Cockcroft-Gault formula (a creatinine-based method of calculating GFR) have shown that in individuals with GFR >90 mL/min/1.73 m^2, these equations significantly underestimate filtration rate and can only be used for patients with established CKD stage G3 and beyond.[17] Because of these limitations, other markers are being investigated for more efficient estimation of GFR. Cystatin C, a plasma protein that is freely filtered and metabolized in tubular cells, is one such marker.[1,18] Initial evaluations indicated that its concentration was independent of age, sex, diet, and muscle mass, but new evidence points to higher levels in males and older individuals, as well as a possible influence from both hyperthyroidism and hypothyroidism.[18] A number of researchers have evaluated cystatin C as a marker for GFR. One study evaluated GFR using a cystatin C–based equation vs creatinine-based equations in 56 patients with type 2 DM. The accuracy of cystatin C was 90% for identifying GFR at rates <80 mL/min compared to creatinine measurements with 77% accuracy.[19] The relationship between cystatin C and GFR was significantly stronger compared to creatinine-based equations.

Although cystatin C is a potential new marker for GFR evaluation, it currently is not widely available and not all assays are universally calibrated.[11,20] Until a universal equation is available, both GFR and albuminuria remain the standard and need to be assessed yearly, if not more frequently, to appropriately evaluate the progression of CKD in DN.[11]

Novel Screening Advancements

New methods are on the horizon for detecting DN. As mentioned earlier, renal damage may have already

occurred in patients with DN without evidence of albuminuria.[5] This possibility presents the concern that a number of individuals who are experiencing renal damage are labeled as stage A1. A new approach in DN screening is being developed that has the potential to identify DN earlier than the standard urine albumin measurements. Urinary proteomics uses capillary electrophoresis coupled with mass spectrometry to identify new urinary protein markers.[21] Using this technique, numerous novel biomarkers (mostly collagen products) have been identified and used to classify DN with high sensitivity (85%) and specificity (97%).[21] Zürbig et al reported the ability to predict DN, on average, up to 1.5 years before the onset of stage A2 albuminuria, and in some patients changes were seen up to 5 years prior.[21] With the potential to identify patients years before significant renal damage has occurred, urinary proteomics shows promise as a screening tool.

Given clinician time constraints, even astute clinicians may overlook an annual screen. As electronic medical record (EMR) systems become the norm in outpatient offices, hopefully adherence to screening recommendations among primary care providers will increase. In current EMR systems, clinicians can establish alerts for patients at specific intervals that will prompt clinicians of annual or multiannual laboratory evaluations prior to the patient leaving the office.

TREATMENT

The risk for developing DN increases with the duration of diabetes and associated comorbidities.[22] Although the need for timely diagnosis of DN cannot be stressed enough, the prompt management of DM is by far the rate-limiting step in the prevention of the disease; simply put, the better the control of DM, the greater the delay of DN.[5,7,8] If albuminuria has already been detected in a patient, prompt management with the goal of reducing the progression to worsening CKD or even ESRD is crucial.[7,8] Treatment should be started aggressively with special attention to known risk factors and comorbidities. The 2 most important are hyperglycemia and hypertension.

Hyperglycemia

Several observational studies have shown a strong relationship between poor glycemic control and microvascular complications.[23,24] Recent large randomized controlled trials have shown the benefit of tight glycemic control on the progression of stage A2 and stage A3 albuminuria.[24] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) was conducted to evaluate the relationship of intensive glucose control with vascular outcomes. In this landmark trial, subjects were randomized into tight glycemic control (hemoglobin A1c $<$6.5%) and standard control. The overall outcome showed a significant reduction in microvascular events. Specifically, ADVANCE showed that a hemoglobin A1c of 6.5% or less led to a 10% risk reduction in combined microvascular and macrovascular events and a 21% relative reduction in nephropathy.[24] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial attempted to investigate the same relationship with regard to cardiovascular risk. This study compared intensive glycemic management (hemoglobin A1c $<$6%) with standard (hemoglobin A1c 7%-7.9%) control. The study was halted because of increased mortality in the intensive control group, but additional analysis showed a significant decrease in albuminuria in the intensive group.[25] Subsequently, Coca et al published a metaanalysis that reviewed the effect of intensive glucose control in the development of renal endpoints. They found that intensive glucose control reduced the risk of progression to stage A2 and A3 albuminuria; however, the investigators were not able to show how the reduced progression to albuminuria related to creatinine elevation, progression to ESRD, and death from renal disease.[23] These trials confirmed that tight glycemic control reduces overall albuminuria. Current guidelines have thus adopted a recommended target goal of a hemoglobin A1c $<$7%, if tolerated, for optimal glycemic control and for the prevention of renal pathology.[7,10,26] Because elderly patients are more prone to complications of hypoglycemia, the risk/benefit of tight hemoglobin A1c regulation should be carefully considered, and a higher hemoglobin A1c goal may be acceptable for this population.[7,8,10,26]

Patients with DM should be advised of the numerous benefits of nonpharmacologic methods to improve glycemic control, such as diet and exercise.[26] ADA recommendations call for a diet rich in whole grains, the reduction of trans fats, and a decrease in the consumption of foods with a high glycemic index.[27] Patients should also be encouraged to participate in at least 150 minutes per week of moderate-intensity aerobic exercise so that diet and exercise have a combined effect on glycemic control.[27] For those who are not able to engage in exercise or who fail nonpharmacologic treatments, a large array of pharmacologic options is available to help with glycemic control. Delving into an exhaustive consideration of all the pharmacologic options for glycemic control is beyond the scope of this paper; instead, we discuss some relatively new treatment modalities.

Table 3: Common Antihyperglycemics and their Potential Adverse Reactions

Class	Drug	Adverse Reactions
Biguanide	Metformin	Gastrointestinal distress, lactic acidosis (rare)
Sulfonylureas	Glyburide, glipizide, glimepiride	Hypoglycemia, weight gain, drug accumulates in renal failure (except glimepiride)
Thiazolidinedione	Rosiglitazone, pioglitazone	Lower extremity edema, heart failure, bone fractures, cardiovascular events, possible liver toxicity
Dipeptidyl peptidase-4 inhibitor	Sitagliptin, saxagliptin, linagliptin, vildagliptin	Possible pancreatitis, angioedema
Glucagon-like peptide-1 analogs	Exenatide, liraglutide	Nausea and vomiting, thyroid C-cell hyperplasia, acute interstitial nephritis
Insulin	Human insulin, aspart, lispro, detemir, glargine, mixed preparations	Hypoglycemia, weight gain

Note: Data extrapolated from Wolf,[2] Schernthaner,[22] Ismail-Beigi,[26] and Zanchi.[28]

Pharmacologic Treatments. Currently, 10 classes of noninsulin treatments are available for glycemic control for patients with type 2 DM. Aside from the common antihyperglycemics such as metformin, sulfonylureas, and thiazolidinediones, newer agents have found their place among the arsenal, and data indicate that the new agents may offer added protection against DN. Dipeptidyl peptidase-4 inhibitors (ie, sitagliptin, saxagliptin, linagliptin, and vildagliptin) and glucagon-like peptide-1 analogues (such as exenatide and liraglutide) are growing in popularity because of their efficacy and tolerability (Table 3).[22,26,28] These incretin therapies have also been shown to slow or even prevent the progression to DN.[22,26] One major advantage of these medications compared to the traditional antihyperglycemics is their safety profile for patients with varying degrees of renal insufficiency. Of these, linagliptin is of particular benefit as it has a nonrenal mode of excretion and can be used in patients with advanced renal disease without dose adjustment.[22,26,28] Another class of agents consists of sodium-glucose cotransporter 2 inhibitors such as canagliflozin and empagliflozin.[29] These agents inhibit the sodium-glucose transporter in the proximal renal tubules where approximately 90% of all glucose is normally reabsorbed. Studies have shown that inhibition of this receptor allows patients with type 2 DM to reduce their weight, improve fasting blood glucose levels, and improve hemoglobin A1c levels through increased urinary glucose excretion, an effect that persisted in patients with reduced renal function.[29] A recent study showed that 8 weeks of empagliflozin resulted in a significant decrease in glomerular hyperfiltration with a concomitant decrease in hemoglobin A1c accompanied by a reduction in insulin use without any change in diet.[30]

One important limitation of these newer agents, however, is their cost.[26] With cost in mind, the following brief review focuses on the more inexpensive therapeutic options with their potential cautions. As pointed out earlier, renal injury in DM often results in a decline in GFR, and once the GFR falls below 60 mL/min/1.73 m^2, the pharmacokinetics of many drugs make dosing particularly challenging.[26] Metformin, which has a preeminently advantageous profile and is the most popular first-line oral antihyperglycemic, is currently advised to be discontinued for patients with a GFR less than 45 mL/min/1.73 m^2 when the possibility of dehydration is looming or when the need of other nephrotoxic agents takes precedence (ie, intravenous contrast) because patients may experience significant lactic acidosis.[26] This recommendation comes from previous studies of an older biguanide, phenformin, that has lactic acidosis as a known complication, although older studies have shown that when switching patients from phenformin to metformin or using metformin vs placebo, the amount of serum p-lactate either decreased or remained unchanged.[31] Extreme caution and expert consultation remain the standard when using metformin with CKD. Another popular medication class, sulfonylureas, is notorious for its risk of hypoglycemia and should be discontinued when the GFR falls below 60 mL/min/1.73 m^2.[26,32] Lastly, thiazolidinediones are limited by their ability to increase water and sodium retention, particularly in patients with renal insufficiency, that can lead to worsening edema and heart failure.[26,32]

Hypertension

Blood pressure management is critical in patients with cardiovascular disease to halt further progression of atherosclerotic changes.[7] DM increases the risk of

cardiovascular disease 2- to 3-fold with every incremental increase in systolic pressure.[33] Additionally, 30%-50% of patients with DM concomitantly suffer from hypertension.[7,8,10] Until recently, guidelines from the ADA and the NKF set a goal blood pressure of <130 mmHg systolic and <80 mmHg diastolic to decrease proteinuria and slow the progression to DN.[7,10,34] Although several studies have suggested that lowering blood pressure beyond a certain point might result in a J curve and actually contribute to increased mortality, the reduction of proteinuria remained a therapeutic goal in several trials. In the ACCORD trial, the blood pressure arm looked at the effects of controlling blood pressure to <120 mmHg systolic and the effect on cardiovascular events.[25] The results indicated that although the intensive control group had a lower frequency of stage A3 albuminuria, it also had significantly higher rates of adverse events and electrolyte imbalances, and, despite lowering the blood pressure, no significant difference in outcome was noted compared to the standard group.[33] The Eighth Joint National Committee currently recommends a blood pressure goal of systolic <140 mmHg and diastolic <90 mmHg in all patients with DM or CKD.[34] The committee concluded that most of the recent literature did not show a significant difference in outcomes between a higher blood pressure goal (<140/90 mmHg) compared to a lower (<130/80 mmHg) and more desirable goal.[34] In a review of randomized controlled trials involving individuals <70 years of age with a GFR <60 mL/min/1.73 m^2 and albuminuria >30 mg/g, lowering the blood pressure goal to <130/80 mmHg did not reduce renal or cardiovascular disease endpoint goals compared to the goal of <140/90 mmHg.[34]

Medications. Over the last decade, using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in the management of DN to decrease albuminuria and thwart the progression of CKD has become standard practice.[12]

Besides these drugs' benefit of lowering blood pressure, their inhibition of the renin-angiotensin-aldosterone system (RAAS) appears to play a pivotal role in the slowing of the progression of stage A2 and stage A3 albuminuria to overt DN.[8,12] Both ACE inhibitors and ARBs reduce blood pressure by decreasing the vasoconstrictive effect of angiotensin 2. Additionally, they reduce fibrous infiltration and inflammatory processes in the glomerulus by blocking secondary pathways.[3] Landmark trials of ACE inhibitors and ARBs have dictated standard practice in the prevention of DN. Captopril, originally studied in patients with insulin-dependent type 1 DM, resulted in a 50% reduction in the endpoints of death, dialysis, and transplant, and it protected against GFR decline when compared to standard blood pressure treatment alone.[35] Losartan, studied in patients with type 2 DM, reduced the incidence of creatinine doubling and decreased proteinuria by 35% compared to conventional antihypertensive medications.[36] Barnett et al compared management with ACE inhibitors to ARBs in patients with type 2 DM. Telmisartan and enalapril were compared in a randomized, double-blind study over a 5-year treatment period, and telmisartan was found to be equivalent to enalapril; both offered significant renal protection.[37]

Dual therapy of an ACE inhibitor and an ARB may further reduce proteinuria because of a potential synergistic effect. Mann et al, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), studied the use of an ACE inhibitor and an ARB—individually and in combination—over a 6-year period.[38] They concluded that the ARB and the ACE inhibitor had similar renal outcomes when used as monotherapy, but dual therapy reduced proteinuria to a greater extent. However, the combination therapy worsened renal outcomes and led to a greater incidence of acute renal insufficiency and hypotension.[38]

The debate over whether dual therapy is superior to monotherapy appears to have finally been put to rest with the publication of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial. This trial evaluated combination ACE inhibitor/ARB therapy and its effects on decreasing proteinuria.[39] The trial was stopped early because of an increasing number of safety concerns. The study demonstrated that the benefit of combination therapy tended to decrease over time, with an increase in adverse events such as hyperkalemia and acute renal failure.[39] Makani et al published a review and metaanalysis on ACE inhibitor/ARB combination therapy that makes a similar point. Although dual therapy demonstrated a decrease in hospital admission for heart failure, it demonstrated no benefit for all-cause mortality or cardiovascular mortality.[40] Additionally, the work of Makani et al showed that dual therapy was associated with a 55% increase in hyperkalemia, a 66% increase in hypotension, a 41% increase in renal failure, and a withdrawal rate of 27% because of adverse events.[40] With no significant change in mortality and with the significant increase in adverse events, these studies argue against the further use of dual therapy for DN management.[39,40]

Regarding the progression of DN, the RAAS pathway is the one most responsible for albuminuria, mesangial expansion, and glomerular fibrosis.[3,12] Current studies are investigating renin inhibitors to stop the cascade before it even begins. A direct renin inhibitor, aliskiren, has been investigated to determine

its ability to aid in the initial blockade of the RAAS.[7,8,12] One study explored the benefit of adding a direct renin inhibitor to an ARB, without a focus on blood pressure lowering effects.[41] This study showed that the combination of aliskiren and an ARB significantly reduced proteinuria in patients with type 2 DM.[41] A second trial, Aliskiren Trial in Type 2 Diabetics Using Cardiovascular and Renal Disease Endpoints (ALTITUDE), was stopped early secondary to the increased risk of renal failure, hyperkalemia, hypotension, and nonfatal stroke when the combination of ACE inhibitor or ARB with aliskiren was used.[42] These studies point to adverse effects associated with aliskiren, but further research should be conducted to find if an alternative drug combination is ideal.

Aldosterone has been implicated in the promotion of renal fibrosis and with increasing blood pressure secondary to sodium retention.[12] Although the use of an ACE inhibitor or ARB inhibits the RAAS pathway, emerging evidence shows that aldosterone levels slowly increase over time in patients taking these medications.[11] In a study conducted by Schjoedt et al, the addition of spironolactone to an ACE inhibitor or ARB significantly reduced albuminuria when compared to placebo.[43] More research needs to be conducted in this field, as long-term outcomes are unknown.

Novel Treatment Potential

Vitamin D therapy has recently received attention as a potential treatment option in DN. Initial mouse studies showed that mice unable to make vitamin D or lacking vitamin D receptors had an increase in RAAS activity and even exhibited significant proteinuria.[44] Another study showed that paricalcitol administration led to reduction of albuminuria in patients with type 2 DM.[45] At present, an ongoing trial is investigating whether calcitriol may have antiproteinuric properties, particularly when combined with RAAS blockade therapy.[46]

The role of inflammation and oxidative stress also has been implicated in the pathophysiology of DN.[2] Bardoxolone methyl, a known antioxidant with prostaglandin-like effect, initially was demonstrated to be beneficial in animal models with ischemic renal failure.[47] However, a patient-based trial was stopped after 9 months because of significant adverse effects: increases in cardiovascular events, blood pressure, and albuminuria.[48]

Vasoconstriction and vasodilatation are physiologic mechanisms that are held in check through a number of variables. Endothelin-1 (ET-1), a peptide responsible for binding to vascular smooth muscle endothelin receptor type A, has potent vasoconstrictor effects along with inflammatory properties. This balance is kept in check by endothelin receptor type B that possesses vasodilator and antiinflammatory effects.[49] Animal studies have pointed to an overproduction of ET-1 in CKD specimens.[49] Current studies are now underway with the potential of augmenting these mechanisms to significantly decrease proteinuria in patients with DN.[49]

PREVENTION

Although interventions are available to delay the onset of albuminuria, clinicians who recognize the risk factors in individuals who might develop DN can institute preventive strategies and potentially improve outcomes.[1,5]

Diet

Diet has always been considered a mode of nonpharmacologic maintenance for DM, and the use of dietary modifications as adjunctive therapy for DN is slowly becoming mainstream. Over the years, animal models have shown that restriction of dietary proteins leads to a decrease in intraglomerular pressures and a reduction of hyperfiltration.[5,10] Other small trials using human models have shown a decrease in the decline of GFR with protein restrictions of 0.6 mg/kg/d.[10] A recent metaanalysis of randomized controlled trials showed that low-protein diets were associated with significant improvement in GFR across all subgroups of patients with DM and DN, regardless of intervention time.[50] A low-protein diet was associated with significant improvement in DN and did not worsen glycemic control or cause malnutrition.[50]

Obesity

Obesity is a proinflammatory state and may put a patient at further risk for DN.[3] The American Heart Association estimates that 154.7 million Americans are overweight (body mass index [BMI] >25 kg/m^2) and of these, 78.4 million are obese (BMI >30 kg/m^2).[51] The prevalence of type 2 DM is closely linked to metabolic syndrome and obesity with an estimated 90% of patients with type 2 DM having excess weight.[52] With about 420 million glucose-intolerant individuals projected worldwide by 2025, the concern for obesity and its related complications is increasingly pertinent.[52] Unfortunately, the cause of obesity is multifactorial and no single method of treatment exists. Clinicians should form a close partnership with their patients and attempt various weight-loss strategies that include frequent short-term goal evaluations and positive affirmations.

Smoking

A recent review of 28 epidemiological studies observed that proteinuria (present in 5%-8% of the

patients studied) and stage A2 albuminuria (present in 8%-15% of the patients studied) was significantly higher in current smokers than in nonsmokers. The rate of proteinuria in current smokers was 2-3 times higher than in lifelong nonsmokers. Nine of the studies included in the analysis showed an increase in GFR in smokers compared to nonsmokers. This analysis suggests that smoking, a known inflammatory modulator, aids in the release of systemic inflammatory markers, thus leading to glomerular hyperinflation, a precursor to glomerular fibrosis.[2,53]

Hyperlipidemia

The use of lipid-lowering medications in DN is gaining attention. DM is considered a coronary disease equivalent, and patients with DM are frequently advised to be on 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors. Until recently, few studies specifically looked at the effects of lipid-lowering medications on renal protection. In the Diabetes Atherosclerosis Intervention Study, 314 participants were evaluated after receiving fenofibrate or placebo; those who received fenofibrate had a slower progression to albuminuria.[54] Abe et al investigated the effects of rosuvastatin on kidney function and oxidative stress in patients with DN and showed that although no significant difference occurred in the change in GFR, the levels of albuminuria were significantly less in the statin group irrespective of blood pressure or lipid levels.[55]

The KDIGO working group recently published recommendations for lipid management in patients with CKD. They recommended initiating statin therapy with or without ezetimibe in all patients younger than 50 years with concomitant CKD and DM and in all patients with CKD older than 50 years, regardless of the coexistence of DM.[56] This recommendation is geared at the prevention of cardiovascular disease and excludes patients on chronic dialysis or transplant recipients.[56] The KDIGO group recommended specific dose adjustments for statins in patients with CKD to ensure safety. In addition, they advocate a "fire and forget" rather than a "treat to target" approach, indicating statin administration without scheduled monitoring rather than statin initiation with dose adjustments based on low-density lipoprotein (LDL) goals.[56] However, further studies are needed in patients with both DM and CKD to determine optimal target LDL levels and the impact of antihyperlipidemic therapy on albuminuria.

CONCLUSION

With early detection, proper screening, and management, the impact of diabetic nephropathy may be better mitigated to lessen its impact on society and healthcare.

KEY POINTS

- Albumin to creatinine ratio should be checked at first void of the day. If abnormal, it should be repeated 2 more times within a 3-6 month period because of albumin variability.
- Screening for diabetic nephropathy should begin 5 years after the initiating treatment in patients with type 1 diabetes and at the time of diagnosis in patients with type 2 diabetes.
- Screening for diabetic neuropathy should be done yearly at a minimum and more often if indicated based on glomerular filtration rate and albuminuria.
- Glucose levels should be controlled with oral antihyperglycemics and/or insulin with a hemoglobin A1c goal $<7\%$.
- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be the first line in management for the prevention and delay of albuminuria.
- Dual therapy with ACE inhibitors and ARBs is no longer recommended.
- Blood pressure is pivotal in the progression of albuminuria: ACE inhibitors or ARBs are to be used first with the addition of another antihypertensive for secondary management, with a goal of $<140/90$ mmHg.
- Lifestyle modification—a low protein diet with guidance from a physician, exercise, and smoking cessation—is paramount.
- Statin therapy should be initiated for all patients >50 years of age with CKD and/or transplant.
- Statin therapy should be initiated in patients <50 years of age with known vascular disease and/or DM.
- Consider patient-centric decisionmaking and continue to be proactive in screening.

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