Welcome to Diabetes Dialogue.

Welcome to this issue of Diabetes Dialogue, dedicated to the diagnosis, management, and treatment of diabetic nephropathy. Dr Mark Molitch, a professor of the Feinberg School of Medicine at Northwestern University in Chicago, provides a case study of a patient who required substantial changes to her treatment schedule after initial examination. This case study provides clinical background for healthcare professionals to help them understand management goals for diabetic nephropathy and the options that can be used to achieve them.

CLINICAL CLOSEUP

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Meeting and maintaining treatment goals for a patient with diabetic nephropathy

INTRODUCTION

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States, accounting for 43% of new cases in 2003. A number of factors affect the development of nephropathy, including racial and genetic susceptibility, blood pressure, intrarenal hemodynamic factors, and metabolic control.

Diabetic nephropathy typically follows a predictable natural history that is similar for type 1 and type 2 diabetes (Figure 1). The earliest clinical evidence of nephropathy is usually the appearance of “low but abnormal levels of albumin” in the urine, referred to as microalbuminuria. Microalbuminuria is defined as a urinary albumin excretion rate (AER) between 30-300 mg/24h (equivalent to 20-200 μg/min on a timed specimen or 30-300 mg/g creatinine on a random sample).
Meeting and maintaining treatment goals for a patient with diabetic nephropathy

Microalbuminuria develops in 30% to 40% of both type 1 and type 2 diabetes patients after approximately 20 years of disease; however, a recent analysis suggests that this risk may be somewhat lower. Urinary albumin levels gradually increase, passing 300 mg/24h (300 μg/mg creatinine), a measure referred to as clinical albuminuria, macroalbuminuria, or overt nephropathy. Some years after the development of clinical albuminuria, the glomerular filtration rate (GFR) begins to fall, and over several years it progresses to ESRD. Recent data have challenged this concept, showing that more than one third of people with diabetes have a significant decrease of GFR to <60 mL/min/1.73 m² without any associated albuminuria.

Limited studies suggest that the rates of fall of GFR are similar in patients with and without albuminuria. Thus, current recommendations now include screening for nephropathy by measurement of urinary albumin excretion (UAE) (generally, the most practical test is a spot urine/creatinine ratio in a random sample of urine taken at an office visit) and estimation of the GFR (eGFR) using one of the validated equations available that are based on serum creatinine, such as the one derived from the Modification of Diet in Renal Disease (MDRD) study.

Figure 1. Natural history of nephropathy in type 1 diabetes mellitus. In the 30% to 35% of patients who develop nephropathy, microalbuminuria generally occurs between 5 and 15 years of duration of diabetes. Over the next ~10 years, there is a 25% to 40% chance of progression to clinical albuminuria. Some time after the onset of clinical albuminuria, the GFR begins to fall, and >90% of patients reach ESRD by 20 years after the onset of clinical albuminuria.

Creatinine clearance

Albumin excretion rate

At present, Dr Molitch remains Principal Investigator of the DCCT follow-up study Epidemiology of Diabetes and Its Complications (EDIC) and the Diabetes Prevention Program follow-up study and is Co-Principal Investigator of the Northwestern Center of the ongoing Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) studies. In addition to editing 6 books and journal volumes, Dr Molitch has authored or coauthored more than 250 original papers, review articles, book chapters, case reports, and other publications. Dr Molitch is currently an Associate Editor of the Year Book of Endocrinology and of the journal Pituitary.
INITIAL VISIT

Presentation
A 59-year-old white female with a 13-year history of type 2 diabetes has had prior problems with weight gain and issues related to diabetes control. She presents as overweight and is taking insulin. Her blood pressure is normal, and she shows no signs of peripheral edema or neuropathy.

Exam and Assessment
• Weight 262 lbs
• Height 5’5”
• BMI 41.9 kg/m²
• BP 120/70 mm Hg
• Blood glucose 180-250 mg/dL
• Total cholesterol 269 (LDL/HDL of 185/46 mg/dL)

Medication
Glycemic Control
• Insulin 70/30 48 U in the morning and 8 U at dinner (adjusted as needed)
Microalbuminuria
• Enalapril 5 mg daily

Investigations
Further investigation revealed the following:
• A1C 8.8%
• Serum creatinine 0.8 mg/dL
• eGFR approximately 78 mL/min/1.73 m² (MDRD equation)
• UAE 960 mg/g creatinine

Discussion
Although the patient’s eGFR is only minimally decreased from the normal range (~120 mL/min/1.73 m²),22 she has a substantial quantity of albumin in her urine, indicating definite diabetic kidney disease. Her elevated A1C is a risk factor for further progression of nephropathy and development of other complications, so she was switched to separate neutral protamine Hagedorn (NPH) and regular insulin, allowing for adjustment of each dose.

FOUR-FOLD VISIT AFTER 3 MONTHS

Presentation
At 3 months the patient feels well, but she is reporting muscle aches that she attributes to the atorvastatin. Glucose levels are now better controlled as a result of the switch from a fixed mixture of 70/30 insulin to separate NPH and regular insulin so that each dose could be adjusted.

Key Patient Data at 3-month Follow-up Exam
BP 128/74 mm Hg
A1C 7.8%
Blood glucose 170-215 mg/dL
UAE 448 mg/g creatinine

*Not FDA approved for albuminuria
Exam and Assessment
- Weight 262 lbs
- BMI 41.9 kg/m²
- BP 128/74 mm Hg
- Blood glucose 170-215 mg/dL
- A1C 7.8%
- Total cholesterol 220 (LDL/HDL 160/48 mg/dL)
- Serum creatinine 0.7 mg/dL
- eGFR approximately 67 mL/min/1.73 m² (MDRD equation)
- UAE 448 mg/g creatinine

Medication
Glycemic Control
- NPH insulin 32 U AM, 26 U PM (average, adjusted as needed)
- Regular insulin 12 U AM, 4 U PM (average, adjusted as needed)

Microalbuminuria
- Enalapril 10 mg daily

Hypercholesterolemia
- Colesevelam 625 mg, 3 tablets twice daily
- Atorvastatin 20 mg daily

Discussion
Because of muscle aches, atorvastatin was stopped, a urinalysis was performed for myoglobin, and she started colesevalam 625 mg, 3 tablets twice daily. Metformin 1000 mg BID (initiated at 500 mg BID, increased to 1000 mg BID over 2 weeks) was added to decrease insulin resistance, and her insulin doses were further modified. Because her BP was normal, her ACE inhibitor dose was not increased.

DECREASING THE DEVELOPMENT AND SLOWING THE PROGRESSION OF DIABETIC NEPHROPATHY ARE UNIVERSAL GOALS FOR IMPROVING THE QUALITY OF LIFE FOR PATIENTS WITH DIABETES.

It is controversial as to whether the urine albumin level should be targeted in therapy. Previous studies have all shown benefit from fixed doses of ACE inhibitors and ARBs in slowing the rate of progression of kidney disease. Some of those trials have also demonstrated that individuals who have the greatest lowering of UAE seem to have the greatest slowing in the progressive fall in GFR. This could be due to either a reduction in the potential nephrotoxicity of the excreted protein or may simply reflect a greater effect on intraglomerular pressure by the medication.

FOLLOW-UP VISIT AFTER 18 MONTHS

Presentation
The patient reports feeling well and has persisted in regular glucose checks and adjustments of insulin doses.

Key Patient Data at 18-month Follow-up Exam
BP 122/72 mm Hg
A1C 6.9%
Blood glucose 95-135 mg/dL
UAE 493 mg/g creatinine

Exam and Assessment
- Weight 250 lbs
- BMI 41.6 kg/m²
- BP 122/72 mm Hg
- A1C 6.9%
- Blood glucose 95-135 mg/dL
- LDL cholesterol 124 mg/dL
- Serum creatinine 0.9 mg/dL
- eGFR 68 mL/min/1.73 m²
- UAE 493 mg/g
- Stress test normal

Medication
Glycemic Control
- NPH insulin 32 U AM and 24 U PM (average, adjusted as needed)
- Regular insulin 2 U AM and none PM (average, adjusted as needed)
- Metformin 1000 mg BID

Microalbuminuria
- Enalapril 10 mg daily

Hypercholesterolemia
- Colesevelam 625 mg, 3 tablets BID

Discussion
The patient has been successful in controlling her glucose and blood pressure, which should help in reducing the rate of progression of kidney disease. No further changes in management were planned. She is unable to tolerate a statin drug, so her LDL cholesterol level has remained above target. One possibility would be to add ezetemibe to her colesevalam, which may reduce her LDL by another 10% to 20%. Because of her very high risk of coronary heart disease, periodic stress testing is also in order.
Summary
Decreasing the development and slowing the progression of diabetic nephropathy are universal goals for improving the quality of life for patients with diabetes. Because the prevalence of type 2 diabetes is projected to increase 122% by 2025, reaching 300 million worldwide, the urgency for discovering ways to control diabetic nephropathy is also increasing. The cumulative risk of clinical albuminuria or overt nephropathy is 12% to 25% after 20 years of either type 1 or type 2 diabetes. Numerous previous studies have shown that without specific interventions, 50% to 80% of subjects with type 1 diabetes who develop sustained microalbuminuria progress to overt nephropathy over a period of 10 to 15 years. More recent studies suggest a lower risk, closer to 25% to 40%. Interestingly, according to a recent analysis, nearly the same percentage (20% to 35%) of subjects with microalbuminuria revert to normoalbuminuria. The fact that only a fraction of patients with type 1 or type 2 diabetes develops nephropathy suggests that there may be a genetic susceptibility that predisposes a subject to nephropathy in the face of other contributing factors, such as poor metabolic control and hypertension.

Several large, prospective, randomized trials have demonstrated the efficacy of improved glycemic control in preventing progression of diabetic kidney disease in persons with type 1 and type 2 diabetes. Such studies include the Diabetes Control and Complications Trial (DCCT) and its follow-up observational study, the Epidemiology of Diabetes Interventions and Complications (EDIC), that included patients with type 1 diabetes, as well as the Kumamoto Study and the United Kingdom Prospective Diabetes Study (UKPDS), which enrolled patients with type 2 diabetes. In these studies, a reduction of A1C levels to approximately 7% was remarkably successful in decreasing the initial development and subsequent progression of microalbuminuria and clinical albuminuria.

Hypertension frequently coexists with diabetes mellitus in adults. The prevalence is greater than 50% in persons with type 2 diabetes, and increases with age. Hypertension is prevalent in about 25% of those with type 1 diabetes. The onset of hypertension in type 1 diabetes appears to be primarily a complication of diabetic nephropathy, whereas in type 2 diabetes, hypertension is frequently present at the time of diagnosis of diabetes, with both being components of the metabolic syndrome. Despite the possible differences in pathophysiology of hypertension in the two types, it is clear that uncontrolled hypertension increases the risk for progressive renal damage in patients with either type of diabetes. ACE inhibitors and ARBs appear to offer benefits for progression of kidney and cardiovascular disease beyond their blood-pressure–lowering effects, and, therefore, should be essential parts of the nephropathy treatment regimen even in the absence of hypertension.

Because a number of studies have shown that chronic kidney disease is associated with a markedly increased risk of macrovascular disease that is further elevated in patients with diabetic kidney disease, reduction of all known risk factors is paramount in this group of high-risk patients. Smoking cessation is critical, and the target for LDL cholesterol should be 70 mg/dL. Blood pressure should be maintained at <130/80 mm Hg, and since glycemic control is also important for managing macrovascular disease, an A1C goal for treatment should be 7% or less. A multipronged approach is necessary to obtain the goals of treatment for patients with diabetes who have chronic kidney disease, and such an approach should include strategies for glycemic, blood-pressure, and lipid control.

Key Learning Points
- Diabetic nephropathy is the leading cause of ESRD in the United States, accounting for 43% of new cases in 2003
- The earliest clinical evidence of nephropathy is microalbuminuria, which is defined as a urinary albumin excretion rate between 30-300 mg/24h
- Urinary albumin levels passing 300 mg/24h are referred to as clinical albuminuria, macroalbuminuria, or overt nephropathy
- Some years after the development of clinical albuminuria, the glomerular filtration rate (GFR) begins to fall, and over several years it progresses to ESRD
- In about one third of patients, a fall in GFR occurs without the prior development of albuminuria, so both the urine albumin level and estimation of the GFR based on serum creatinine should be performed annually as screening tests
- ACE inhibitors and ARBs appear to offer benefits for progression of kidney and cardiovascular disease beyond their blood-pressure–lowering effects, and, therefore, should be essential parts of the nephropathy treatment regimen
- A multipronged approach is necessary to obtain the goals of treatment for patients with diabetes who have chronic kidney disease
Hypertension treatment guidelines: practical implications.


Guidelines for treatment and management of hypertension are designed to assist physicians in reducing the risk of cardiovascular (CV) and renal events among their patients. The committees that develop such guidelines research published clinical trials and opinions from experts in the specific fields that are relevant. A recently published article provides reviews of guidelines for blood pressure control and treatment of kidney disease produced by the American Diabetes Association (ADA), the Kidney Disease Outcome Quality Initiative (K/DOQI), the European Society of Hypertension (ESH), and the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Lowering blood pressure (BP) can provide several advantages, including reduction of the risk for renal and CV events. Several guidelines for clinical practice are available, and although most of them agree on essential issues, some differences do exist (see Table 1). For example, since the risk of CV events doubles with each 20 mm Hg increase in systolic blood pressure, JNC 7 has recommended paying special attention to prehypertension, defined as BP >120 and <140 mm Hg.

A goal of treatment for patients with hypertension should be obtaining systolic and diastolic BP of <140 and <90 mm Hg, respectively. Patients who have diabetes or a kidney disease require even lower BP, and their objectives should be <130 and <80 mm Hg. Several reports provided by experts have demonstrated the benefits of reaching such goals. The United Kingdom Prospective Diabetes Study (UKPDS) reported that improved BP control reduces CV outcomes, and patients who achieved 144/82 mm Hg had 24% fewer diabetes-related endpoints, 32% fewer deaths, 44% fewer strokes, and 37% fewer microvascular complications than patients with an average BP of 153/87. The Hypertension Optimal Treatment study found greatest reductions in CV events among patients with diastolic BP below 80 mm Hg, and the National Kidney Foundation (NKF) reported marked reductions in both CV and kidney disease in patients with systolic BP <130. Both the UKPDS and the Hypertension Optimal Treatment group have proven that intensive BP lowering is not harmful for patients.

Modifications in lifestyle can also provide substantial benefits for patients. Most guidelines recommend that obese patients who are hypertensive lose weight and that all patients reduce sodium intake to 100 mmol and alcohol consumption to 2 drinks or fewer per day. In addition, cessation of smoking reduces the BP increase it causes, and exercise for those for whom it is safe can benefit all patients with hypertension. Patients who do not meet the objectives necessary for reducing the risk of CV events by making lifestyle changes alone usually require pharmacological interventions.

The reduction of CV events and renal morbidity and mortality are the ultimate goals of hypertension treatment, and achieving BP control in the least intrusive fashion should be the short-term goal. Several factors can be considered intrusive, including economic impact, necessary office visits, adverse events, and inconvenience. Most patients must receive more than one treatment, as reported by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which found that among patients obtaining BP <140/90 mm Hg, 60% required 2 or more antihypertensive agents. ALLHAT also revealed groups receiving a thiazide-like diuretic drug, calcium antagonist, α-blocker, or angiotensin-converting enzyme (ACE) inhibitor had no differences in congestive heart disease, death, or nonfatal myocardial infarction; however, the thiazide-like diuretic drug was significantly better than others at preventing heart failure and reducing BP, stroke, and CV events. The JNC 7 group, therefore, recommended that a thiazide-like diuretic be used as an initial antihypertensive for most patients with stage 1 hypertension. Older patients can have diuretic treatment initiated with an ACE inhibitor, angiotensin II receptor blocker (ARB), β-blocker, or calcium antagonist, or several

<table>
<thead>
<tr>
<th>Similarities</th>
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<tbody>
<tr>
<td>Achievement of a specific BP goal (&lt;140 mm Hg in the general population and &lt;130/80 mm Hg if diabetes or chronic kidney disease is present)</td>
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<tr>
<td>Support ≥2 agents if goal BP not achieved after dose adjustment of 1 agent</td>
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<tr>
<td>Reduced cardiovascular morbidity and mortality as endpoint of BP reduction</td>
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<tr>
<td>Focus on special populations and specific goals, if any, in those groups</td>
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<td>All emphasize lifestyle intervention</td>
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<table>
<thead>
<tr>
<th>Differences</th>
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<tbody>
<tr>
<td>Definitions of risk for various BP differ, especially at the lower end of the scale (eg, prehypertension in JNC 7 and other guidelines)</td>
</tr>
<tr>
<td>Approach to care: although all support use of ACE inhibitors or ARBs for those with kidney disease, or diabetes and β-blockers for those with CAD, the JNC 7 specifically supports thiazide diuretics as initial agents for achieving goal BP in most people in the general population, defined as those older than 55 years</td>
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ACE = Angiotensin Converting Enzyme, ARB = Angiotensin Receptor Blocker, BP = Blood Pressure, CAD = Coronary Artery Disease, JNC = Joint National Committee
fixed-dose combinations of diuretics that currently exist. Kidney dysfunction can also be treated by lowering BP, which slows progression of nephropathy. The Modification of Diet and Renal Disease study showed progression to end-stage renal disease (ESRD) was reduced when mean arterial BP reached 92 mm Hg. ACE inhibitors and ARBs can slow progression of diabetic and nondiabetic nephropathy when BP is <140/90 mm Hg. A combination of hypertension and diabetes induces a greater risk of CV events and renal failure than either factor alone, so patients with type 1 diabetes should receive a blocker of the renin-angiotensin system and a diuretic agent. Patients with type 2 diabetes should achieve BP goals and receive a blocker of the renin-angiotensin system, such as an ARB. The JNC, ADA, and the NKF have stated that a nondihydropyridine (DHP) can be used as a third-line therapy once a diuretic along with an ACE inhibitor or ARB has been tried.

Coronary artery disease (CAD) is a major risk factor among patients with hypertension, and both β-blockers and calcium antagonists are effective antihypertensive agents often preferred for initial treatment. Renal insufficiency is an independent risk factor for death among patients with CV disease. After acute myocardial infarction, patients with ESRD have a 5-fold increase of both in-hospital and postdischarge deaths compared with patients who have normal renal function. In contrast, mild renal insufficiency, defined as creatinine clearance from 50 to 75 mL/min, results in only a 2-fold increase in risk of in-hospital and postdischarge deaths. In spite of risk of fatality, the United States Renal Data System has concluded that treatment for CV disease risk factors is poor among patients on kidney dialysis, with only 18% receiving aspirin, 21.9% receiving ACE inhibitors, and 9.2% received statins.

Once 4 years have elapsed, fewer than 50% of patients have continued initially prescribed antihypertensive agents. Approximately 10% of hypertension expenditures in the United States are wasted as a result of nonadherence to medical advice and drug therapy. Lifestyle management is often insufficient, and medications are often indicated for patients with hypertension (BP >140/90 mm Hg), diabetes, and renal disease with BP >130/80 mm Hg. Multiple treatments are required for many patients, including those with renal disease and nephropathy, those with systolic BP 20 mm Hg higher than the goal, and those with diastolic BP more than 10 mm Hg higher.

**Preserve-β: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin.**


Type 2 diabetes is characterized by a deterioration of β-cell function, which necessitates the use of multiple agents to maintain adequate glycemic control. Nateglinide and glyburide are two agents that may be used to combat diabetes-related β-cell dysfunction. The purpose of this study was 2-fold: 1) to test the hypothesis that the combination of nateglinide and metformin will provide glycemic control with a decreased incidence of hyperglycemia and weight gain compared with the combination of glyburide and metformin, and 2) to compare the 2-year efficacy of nateglinide/metformin and glyburide/metformin in type 2 diabetes patients.

A total of 428 subjects with type 2 diabetes participated in this randomized, multicenter, 2-year study. Inclusion criteria included: 1) drug-naïve patients, 2) aged 18-77, 3) baseline A1C between 7.0% and 11.0%, 4) fasting plasma glucose (FPG) ≤15 mmol/L, and 5) BMI between 22 and 45 kg/m². Patients were randomized into one of 2 groups: 1) a combination therapy group with nateglinide plus metformin (Nate/Met group), or 2) a combination therapy group with glyburide plus metformin (Glyb/Met group). Each treatment group had a corresponding placebo group. Treatment for the first 4 weeks consisted of either 120 mg AC nateglinide or 1.25 mg glyburide before breakfast and 200 mg open-label metformin before the evening meal, followed by a 12-week titration period, during which patients received either 120 mg AC nateglinide or treatment with glyburide (titrated to a maximum of 10 mg daily in 1.25 mg increments) and...
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metformin titrated to a maximum of 2000 mg daily, as necessary. An 88-week monitoring period followed. A1C, glycemic control, postprandial glucose excursions (PPGE), and FPG were measured at Weeks -2, 0, and 4 and again at Weeks 20, 28, 40, 52, 64, 76, 88, 96, and 104.

The results from the 2 groups were similar in terms of glycemic control. The mean change in A1C from baseline was -1.2 ± 0.1% in the Nate/Met group and -1.5 ± 0.1% in the Glyb/Met group \((P = .1730)\). A total of 39% of the Nate/Met group and 43% of the Glyb/Met groups had maintained the American Diabetes Association’s recommended A1C goal of ≤7.0% at the end of 2 years. The mean change in FPG from baseline to week 104 was -0.6 ± 0.2 mmol/L in the Nate/Met group \((P < .0001)\) and -2.4 ± 0.2 mmol/L in the Glyb/Met group.

Although the results were similar in terms of glycemic control, there were some important differences observed in terms of side effects. Body weight in the Nate/Met group decreased slightly \((\Delta = -4.0 ± 0.4 \text{ kg})\), whereas body weight in the Glyb/Met group increased slightly \((\Delta = 0.8 ± 0.5 \text{ kg})\). This difference was statistically significant. One or more episodes of hypoglycemia were reported by 8.2% of the Nate/Met group vs 17.7% of the Glyb/Met group \((P = .003)\).

The results of this trial suggest that combination therapy with an insulinotropic and an insulin-sensitizing agent is an efficacious method for maintaining glycemic control. Within this study, both the Nate/Met and the Glyb/Met groups produced similar results. It should be noted, however, that the Glyb/Met group exhibited a more than 2-fold incidence of hypoglycemia in relation to the Nate/Met group.

Angiotein-converting enzyme inhibitors or angiotensin II receptor blockers for prevention and treatment of nephropathy associated with type 2 diabetes mellitus.


The American Diabetes Association (ADA) recommends controlling both glucose and blood pressure for reducing the risk of developing diabetic nephropathy and for slowing the progression once it develops. Patients with type 1 diabetes can receive angiotensin-converting enzyme (ACE) inhibitors to delay the onset of end-stage renal disease (ESRD), address hypertension, and target albuminuria. Angiotensin II receptor blockers (ARBs) can be used to prevent or treat diabetic nephropathy among patients with type 2 diabetes, as well as to address hypertension and macroalbuminuria, although their use has been questioned. No direct comparisons of the efficacy of ACE inhibitors and ARBs for treatment of nephropathy among patients with type 2 diabetes have been completed. The authors of this paper reviewed the pathophysiology of the disease, as well as the effects of ACE inhibitors and ARBs on the renin-angiotensin-aldosterone system (RAAS), the clinical evidence of prevention and treatment with those compounds, the use of microalbuminuria as a marker (see Table 2), and recommendations for drug therapy from organizations that are focused on diabetes care.

Both ACE inhibitors and ARBs affect RAAS and can, therefore, lower blood pressure.

Detection of microalbuminuria is the most commonly used procedure for diagnosing diabetic nephropathy and measuring its progression. Most patients with type 1 diabetes do not have microalbuminuria within the first 5 years of onset of their disease, whereas preexisting hypertension and subclinical hyperglycemia occur in 20% to 50% of patients with type 2 diabetes who have microalbuminuria present at the time of their initial diagnosis. A range of 2.6% to 11% of patients with type 2 diabetes progresses from microalbuminuria to clinical albuminuria each year, and another 3.4% to 5.6% proceed from that stage to ESRD. Sustained hyperglycemia is the most likely cause of diabetic kidney damage, including mesangial expansion and thickening of the glomerular basement membrane. Once the glomerular basement membrane is damaged, the negatively charged plasma proteins, such as albuminuria, that healthy glomerular basement membranes can repel are able to pass into the Bowman space and urine, resulting in microalbuminuria. The mesangium is the thin membrane that acts as connective tissue to support capillaries in the renal glomerulus mesangium. Once there is mesangial expansion, resulting pressure exerted on the glomeruli causes reductions in renal function that is evidenced by decreased creatinine clearance. Since data obtained at the onset of hyperglycemia among patients with type 2 diabetes are obscure, further study is needed to determine if the progression of pathophysiologic processes is
comparable to that among patients with type 1 diabetes. Glomerular cells secrete renin in order to convert angiotensinogen to angiotensin I, which is then cleaved by ACE to form angiotensin II, a constrictor of peripheral arterioles that causes systemic vascular restriction. Angiotensin II also constricts efferent glomerular arterioles, thereby increasing the pressure within them and damaging the basement membrane. Both ACE inhibitors and ARBs produce renoprotective effects, including dilation of the efferent arterioles, reductions of intraglomerular pressure, and decreases of urinary protein excretion. They also act on RAAS, thereby lowering blood pressure. Studies designed to measure the efficacy of both ACE inhibitors and ARBs for patients with type 2 diabetes have demonstrated benefits provided by those treatments.

Several studies have revealed the efficacy with which ACE inhibitors can reduce the risk of progression to microalbuminuria among patients with type 2 diabetes. The results of the Microalbuminuria, Cardiovascular, and Renal Outcomes in Heart Outcomes Prevention Evaluation (MICRO-HOPE) study include a statistically significant 24% reduction in the risk of progression to clinical albuminuria. Patients in the Bergamo Nephrologic Diabetic Complications Trial (BENEDICT) had significant reductions in blood pressure, as well as lower rates of progression to microalbuminuria. Reduction in urinary albumin excretion (UAE) has also been demonstrated in ACE inhibitor trials.

ARBs have been shown to reduce UAE, as well as decrease the incidence of other renal outcomes. The Microalbuminuria Reduction with Valsartan in Patients with Type 2 Diabetes (MARVAL) trial revealed decreased UAE and reduced systemic blood pressure, and the Irbesartan in Diabetic Nephropathy Trial (IDNT) demonstrated reductions of UAE, doubling of the serum creatinine levels, onset of ESRD, and death. The albumin:creatinine ratio, as well as doubling of the serum creatinine level, ESRD, and death from any cause were also significantly decreased in the Reduction of End Points in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trial. Two studies designed to compare the efficacy of ACE inhibitors and ARBs did not reveal significant differences among patients with type 2 diabetes, but several smaller trials did demonstrate some slight benefits, such as slowing progression from microalbuminuria to clinical albuminuria, when the two medications were administered in combination.

Although their mechanisms of action differ, both ACE inhibitors and ARBs affect RAAS and can, therefore, lower blood pressure. They serve as renoprotectors by reducing pressure within the glomeruli, and have been shown to be effective for patients with type 2 diabetes. Further research may provide insight regarding adjunctive or sequential administration of those compounds.

Table 2. Methods for detecting microalbuminuria

<table>
<thead>
<tr>
<th>Category</th>
<th>24-Hour (mg/day)</th>
<th>Timed (μg/day)</th>
<th>Spot (μg of albumin/mg of creatinine)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30-299</td>
<td>20-199</td>
<td>30-299</td>
</tr>
<tr>
<td>Clinical albuminuria</td>
<td>≥300</td>
<td>≥200</td>
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Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study.


Because of the progressive β-cell decline associated with type 2 diabetes, many patients will eventually require insulin therapy. Because of a variety of patient and healthcare practitioner factors, insulin therapy for patients with type 2 diabetes often is not initiated in a timely manner. Previous research suggests that patients are resistant to insulin therapy for several reasons, including: belief that insulin is associated with undesirable effects (eg, weight gain, hypoglycemia, complications), belief that insulin therapy initiation is a sign of patient failure, fear that insulin therapy is accompanied by lifestyle limitations and social stigma, and skepticism that insulin therapy will improve diabetes management. In terms of physician attitudes regarding insulin therapy initiation, little is known. Furthermore, attitudes toward insulin may vary by geographic location. The goal of this report was to describe patient and healthcare provider attitudes toward insulin therapy initiation and factors related to those attitudes in a large multinational sample of patients with diabetes and healthcare providers.

Data used in this report were collected as part of the Diabetes Attitudes, Wishes, and Needs (DAWN) study. The DAWN study included participants from 11 regions, including Australia, France, Germany, India, Japan, the Netherlands, Poland, Scandinavia, Spain, the United Kingdom, and the United States. There were 3 separate samples of respondents analyzed in this report: physicians who were treating at least 5 patients with type 2 diabetes per month (n = 2,681), nurses who were treating at least
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5 patients with type 2 diabetes per month (n = 1,109), and adults with self-reported diabetes and who were not currently using insulin (n = 2,061). The primary outcome measure for healthcare providers was insulin initiation delay. Predictor variables included demographics and a variety of provider characteristics, including: professional roles, percentage of diabetic patients with type 2 diabetes, perceived patient psychological distress, perceived patient adherence, perceptions of patient attitudes toward insulin, provider beliefs about insulin efficacy and financial barriers, and provider attitude toward delay of oral hypoglycemic medications. The primary patient dependent variables included perceived efficacy for insulin and self-blame for insulin. Patient demographics, disease characteristics, self-reported adherence, perceived diabetes control, diabetes-related distress, and quality of relationship with healthcare provider were also assessed.

In terms of sample characteristics, physicians were predominantly male, and nurses were mainly female. The 2 provider groups had similar views on patient adherence and patient attitudes toward insulin therapy. Both provider groups were found to delay initiation of oral therapy and insulin. On average, patient participants were middle-aged people who had diabetes for 8 years. Healthcare professionals and patients rated all measurements as “high” or “low.” Patients had a higher self-reported efficacy for appointment keeping and medication taking than for diet and exercise. Delay of insulin was longer than delay of oral medications, and patient beliefs regarding the perceived efficacy of insulin therapy were low, while self-blame for having to take insulin was high. Healthcare provider delay of insulin therapy was longer in the United States than in most other countries. Specialists and practitioners who believed insulin to be efficacious were less likely to delay insulin therapy initiation.

The results of this study demonstrate that there is a high level of resistance to the initiation of insulin therapy among both patients and healthcare providers. In fact, healthcare providers are not just resistant to initiating insulin therapy, but, rather, show a pattern of reluctance to prescribe antihyperglycemic medications in general. This report highlights a number of important patient findings as well, including the high level of self-blame and the low level of perceived efficacy of insulin that were common among patients with type 2 diabetes in this multinational sample. The DAWN study is an important step in overcoming the barriers associated with advancing therapy for people with type 2 diabetes. By identifying patient and healthcare provider attitudes that negatively affect treatment advancement, more informed interventions to address these attitudes can be developed in the future.

Specialists and practitioners who believed insulin to be efficacious were less likely to delay insulin therapy initiation. The rising prevalence of diabetes in the United States, along with extensive potential morbidity and excessive healthcare costs, has resulted in greater burdens on patients and professionals who provide their care. A continuum of diabetes care provides great benefits and is applicable in inpatient and outpatient settings. Effective inpatient care can improve hospital outcomes for patients with diabetes, and structured and integrated outpatient care can lead to decreased use of health services and fewer hospitalizations. Patients who do not receive outpatient follow-up are more likely to experience severe hyperglycemia and the resulting increased risk for complications.

A retrospective analysis of the pattern of postdischarge visits, and an assessment of the characteristics of patients who do and do not participate in follow-up visits were conducted to determine how frequently those visits occur among patients with diabetes in an urban setting. Certified diabetes nurse educators completed questionnaires for patients from a hospital in urban Atlanta that is associated
with outpatient specialty clinics, a diabetes specialty clinic, hospital-based and neighborhood primary care settings, and an emergency department/urgent care center. The questionnaire was used to acquire data pertaining to demographics, date of admission, and date of diabetes diagnosis, as well as admission and discharge glucose values and hyperglycemia medications necessary upon discharge.

Records from 658 patients were included; their mean age at time of initial hospital admission was 49 years, 65% were discharged with insulin, 52% had no health insurance, and 34% had new-onset diabetes or were diagnosed during the hospital stay. The mean glucose was 426 mg/dL at admission and 199 mg/dL at discharge, and mean A1C was 10.5%.

Patients admitted with new-onset diabetes were younger (46 vs 49 years, \( P = .008 \)), had higher blood glucose (533 vs 372 mg/dL, \( P < .001 \)), were predominantly male (59% vs 50%, \( P = .04 \)), and were more likely to be uninsured (63% vs 49%, \( P = .02 \)). The data obtained during that study also revealed that 69% of the patients had their first postdischarge follow-up at an outpatient clinic, 15% had acute care follow-up, and 16% had no follow-up. The average time between discharge from the institutions and any follow-up visit was 7 weeks. A significantly greater percentage of patients were discharged with insulin (\( P = .03 \)), and a significantly greater proportion who would have been required to pay did not participate in follow-up visits (\( P < .001 \)). Patients who did attend postdischarge visits were more likely to be seen in a specialty diabetes clinic (43%) than in a primary care facility (26%). Older patients were less likely to return to the acute care facility (\( P = .04 \)), as were patients with partial (\( P = .005 \)) or no discount (\( P < .001 \)).

The results of this study reveal that most patients attended an initial postdischarge visit, but a substantial portion did not participate in follow-up visits. The authors concluded that new efforts should be conducted to track patients with diabetes after they are discharged to assure that optimal care is maintained and efficient transfer to outpatient settings is achieved.

**Effective inpatient care can improve hospital outcomes for patients with diabetes.**

The Feedback Forum is an opportunity for you to contribute to *Diabetes Dialogue*. Please e-mail us at dialogue@caringfordiabetes.com if you’d like to share your comments and questions. (Due to potential volume, all questions may not be answered.)

**What criteria are recommended for determining when patients with diabetic nephropathy require treatment?**

The American Diabetes Association (ADA) has recommended optimal control of glucose and blood pressure for all patients to reduce the risk of developing diabetic nephropathy and to slow the progression once it develops. Patients should receive additional treatment if they have hypertension, microalbuminuria, or renal insufficiency, which is detected by estimating the glomerular filtration rate from the serum creatinine.

**Which method of screening for microalbuminuria is the most effective?**

The measurement of the albumin-to-creatinine ratio in a random spot collection is the preferred method recommended by the ADA. Options also include a 24-hour collection with creatinine that allows for simultaneous measurement of creatinine clearance, a timed 4-hour collection, or an overnight collection. A patient who has elevated levels detected by any of these tests 2 out of 3 times during a 6-month period has microalbuminuria.

**What treatments should be used for diabetic nephropathy?**

Protein intake should be restricted to ≤0.8 g/kg\(^1\) body wt \(^1\)/day (~10% of total daily calorie intake) for all patients with diabetic nephropathy. Patients with type 1 diabetes who have hypertension and any degree of albuminuria may receive ACE inhibitors to delay the progression of nephropathy. ACE inhibitors and ARBs delay the progression to macroalbuminuria (spot urine collection >300 μg/mg creatinine) among patients with type 2 diabetes, hypertension, and microalbuminuria.

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CLINICAL CLOSEUP REFERENCES


CME POST TEST

CME credit/verification is offered upon successful completion of the post test, as determined by a score of 70% or better. CME certificates will be issued to participants after receipt of the CME demographic and evaluation form and successfully completed post test.

Please record your post-test answers on the adjacent CME demographic and evaluation form.

1) Which of the following usually is the earliest laboratory evidence of diabetic nephropathy?
   a) Appearance of low, but abnormal, levels of albumin in the urine
   b) Fluctuations of levels of albumin in the urine
   c) Sharp decreases in levels of albumin in the urine
   d) Any of the above

2) Which of the following urinary albumin excretion rates obtained from a timed specimen indicates microalbuminuria?
   a) <20 mg/g creatinine
   b) 30-300 mg/g creatinine
   c) 300-450 mg/g creatinine
   d) >450 mg/g creatinine

3) What portion of the type 2 diabetes patient population has glomerular filtration rate (GFR) <60 mL/min/1.73 m² without any associated albuminuria?
   a) >75%
   b) >50%
   c) >33%
   d) <25%

4) Up to 25% of patients have clinical albuminuria or overt nephropathy after they have had type 1 or type 2 diabetes for 20 years.
   a) False
   b) True

5) Patients with diabetic nephropathy are at an increased risk for which of the following?
   a) Myocardial infarction
   b) Stroke
   c) Peripheral vascular disease
   d) All of the above

6) When specific interventions are not employed, up to 40% of patients with type 1 diabetes who have sustained microalbuminuria progress to overt nephropathy. What percentage of patients with type 1 diabetes with microalbuminuria actually revert back to normoalbuminuria?
   a) 40% to 60%
   b) 20% to 35%
   c) 10% to 20%
   d) 5% to 10%

7) Among patients with type 2 diabetes, which of the following is correct?
   a) Hypertension affects less than half
   b) Hypertension may or may not increase risk of renal damage
   c) Diabetes always precedes hypertension
   d) Diabetes and hypertension are components of the metabolic syndrome

8) In addition to lowering blood pressure, treatment with angiotensin converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) have been shown to do which of the following?
   a) Reduce the levels of albuminuria and retard the progression of nephropathy
   b) Reduce the likelihood of developing kidney disease
   c) Provide benefits only for patients with diabetes who have hypertension
   d) Reduce the incidence of kidney disease

9) Which of the following treatment goals are ideal for reducing the risk of chronic kidney disease and the related increased risk of macrovascular disease?
   a) LDL cholesterol <70 mg/dL, blood pressure <140/90 mm Hg
   b) LDL cholesterol <100 mg/dL, blood pressure <140/90 mm Hg
   c) LDL cholesterol <70 mg/dL, blood pressure <130/80 mm Hg
   d) LDL cholesterol <100 mg/dL, blood pressure <130/80 mm Hg

10) The Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that reducing A1C to 7% can do which of the following for patients?
    a) Decrease the initial development of microalbuminuria
    b) Decrease the initial development of clinical albuminuria
    c) Decrease the subsequent progression of microalbuminuria
    d) Decrease the initial development and subsequent progression of microalbuminuria and clinical albuminuria

Thank you for your participation.
**PARTICIPANT INFORMATION** (Please print clearly; illegible forms will delay your receiving credit/verification)

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Please rate the level to which this educational activity has enhanced your professional effectiveness by improving your ability to communicate with and treat/manage patients. 

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In an effort to assess the overall effectiveness of our CME program we plan to survey a convenience sample of participants at 3 months and 1 year to assess the ongoing educational effectiveness of this activity. Please indicate your preferred method of contact:

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