Diabetic Nephropathy

AMERICAN DIABETES ASSOCIATION

Diabetes has become the most common single cause of end-stage renal disease (ESRD) in the U.S. and Europe; this is due to the facts that *1)* diabetes, particularly type 2, is increasing in prevalence; *2)* diabetes patients now live longer; and *3)* patients with diabetic ESRD are now being accepted for treatment in ESRD programs where formerly they had been excluded. In the U.S., diabetic nephropathy accounts for about 40% of new cases of ESRD, and in 1997, the cost for treatment of diabetic patients with ESRD was in excess of $15.6 billion. About 20–30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy, but in type 2 diabetes, a considerably smaller fraction of these progress to ESRD. However, because of the much greater prevalence of type 2 diabetes, such patients constitute over half of those diabetic patients currently starting on dialysis. There is considerable racial/ethnic variability in this regard, with Native Americans, Hispanics (especially Mexican-Americans), and African-Americans having much higher risks of developing ESRD than non-Hispanic whites with type 2 diabetes. Recent studies have now demonstrated that the onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication. This position statement is based on recent review articles that discuss published research and issues that remain unresolved and provides recommendations regarding the detection, prevention, and treatment of early nephropathy.

NATURAL HISTORY OF DIABETIC NEPHROPATHY —
The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels ($\geq$ 30 mg/day or 20 μg/min) of albumin in the urine, referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient nephropathy. Without specific interventions, ~80% of subjects with type 1 diabetes who develop sustained microalbuminuria have their urinary albumin excretion increase at a rate of ~10–20% per year to the stage of overt nephropathy or clinical albuminuria ($\geq$300 mg/24 h or $\geq$200 μg/min) over a period of 10–15 years, with hypertension also developing along the way. Once overt nephropathy occurs, without specific interventions, the glomerular filtration rate (GFR) gradually falls over a period of several years at a rate that is highly variable from individual to individual (2–20 ml · min^{-1} · year^{-1}). ESRD develops in 50% of type 1 diabetic individuals with overt nephropathy within 10 years and in >75% by 20 years.

A higher proportion of individuals with type 2 diabetes are found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for many years before the diagnosis is made and also because the presence of albuminuria may be less specific for the presence of diabetic nephropathy, as shown by biopsy studies. Without specific interventions, 20–40% of type 2 patients with microalbuminuria progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only ~20% will have progressed to ESRD. Once the GFR begins to fall, the rates of fall in GFR are again highly variable from one individual to another, but overall, they may not be substantially different between patients with type 1 and patients with type 2 diabetes. However, the greater risk of dying from associated coronary artery disease in the older population with type 2 diabetes may prevent many with earlier stages of nephropathy from progressing to ESRD. As therapies and interventions for coronary artery disease continue to improve, however, more patients with type 2 diabetes may be expected to survive long enough to develop renal failure.

In addition to its being the earliest manifestation of nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 diabetes. Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all cardiovascular risk factors (e.g., lowering of LDL cholesterol, antihypertensive therapy, cessation of smoking, institution of exercise, etc.). In addition, there is some preliminary evidence to suggest that lowering of cholesterol may also reduce the level of proteinuria.

SCREENING FOR ALBUMINURIA —
A routine urinalysis should be performed at diagnosis in patients with type 2 diabetes. If the urinalysis is positive for protein, a quantitative measure is frequently helpful in the development of a treatment plan. If the urinalysis is negative for protein, a test for the presence of microalbumin is necessary. Microalbuminuria rarely occurs with short duration of type 1 diabetes; therefore, screening in individuals with type 1 diabetes should begin after 5 years' disease duration. Some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore, clinical judgement should be exercised when individualizing these recommenda-

Table 1—*Definitions of abnormalities in albumin excretion*

Category	24-h collection (mg/24 h)	Timed collection (μg/min)	Spot collection (μg/mg creatinine)
Normal	<30	<20	<30
Microalbuminuria	30–299	20–199	30–299
Clinical albuminuria	≥300	≥200	≥300

Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, marked hypertension, pyuria, and hematuria may elevate urinary albumin excretion over baseline values.

tions. Because of the difficulty in precise dating of the onset of type 2 diabetes, such screening should begin at the time of diagnosis. After the initial screening and in the absence of previously demonstrated microalbuminuria, a test for the presence of microalbumin should be performed annually.

Screening for microalbuminuria can be performed by three methods: 1) measurement of the albumin-to-creatinine ratio in a random spot collection; 2) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and 3) timed (e.g., 4-h or overnight) collection. The first method is often found to be the easiest to carry out in an office setting and generally provides accurate information; first-void or other morning collections are preferred because of the known diurnal variation in albumin excretion, but if this timing cannot be used, uniformity of timing for different collections in the same individual should be employed. Specific assays are needed to detect microalbuminuria because standard hospital laboratory assays for urinary protein are not sufficiently sensitive to measure such levels. Microalbuminuria is said to be present if urinary albumin excretion is ≥30 mg/24 h (equivalent to 20 μg/min on a timed specimen or 30 mg/g creatinine on a random sample) (Table 1). Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevations in urinary albumin excretion. If assays for microalbuminuria are not readily available, screening with reagent tablets or dipsticks for microalbumin may be carried out, since they show acceptable sensitivity (95%) and specificity (93%) when carried out by trained personnel. Because reagent strips only indicate concentration and do not correct for creatinine as the

spot urine albumin-to-creatinine ratio does, they are subject to possible errors from alterations in urine concentration. All positive tests by reagent strips or tablets should be confirmed by more specific methods. There is also marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3–6 month period should show elevated levels before designating a patient as having microalbuminuria. An algorithm for microalbuminuria screening is given in Fig. 1.

The role of annual urine protein dipstick testing and microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy and blood pressure control. Many experts recommend continued surveillance both to assess response to therapy and progression of disease. In addition to assessment of urinary albumin excretion, assessment of glomerular function is important in patients with diabetic kidney disease.

EFFECT OF GLYCEMIC CONTROL

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown definitively that intensive diabetes therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in people with diabetes. The glycemic control recommendations for all patients with diabetes in the American Diabetes Association's "Standards of Medical Care for Patients with Diabetes Mellitus" should be followed in this regard.

HYPERTENSION CONTROL

In patients with type 1 diabetes, hypertension is usually caused by underlying diabetic nephropathy and typically becomes manifest about the time that patients develop microalbuminuria. In patients with type 2 diabetes, hypertension is present at the time of diagnosis of diabetes in about one-third of patients. The common coexistence of glucose intolerance, hypertension, elevated LDL cholesterol and triglycerides, and a reduction in HDL cholesterol, obesity, and susceptibility to cardiovascular disease suggests that they may relate to common underlying mechanisms, such as insulin resistance; and this complex is often referred to as syndrome X and/or the metabolic syndrome. Hypertension in type 2 patients may also be related to underlying diabetic nephropathy, be due to coexisting "essential" hypertension, or be due to a myriad of other secondary causes, such as renal vascular disease. Isolated systolic hypertension has been attributed to the loss of elastic compliance of atherosclerotic large vessels. In general, the hypertension in patients with both types of diabetes is associated with an expanded plasma volume, increased peripheral vascular resistance, and low renin activity.

Both systolic and diastolic hypertension markedly accelerate the progression of diabetic nephropathy, and aggressive antihypertensive management is able to greatly decrease the rate of fall of GFR. Appropriate antihypertensive intervention can significantly increase the median life expectancy in patients with type 1 diabetes, with a reduction in mortality from 94 to 45% and a reduction in the need for dialysis and transplantation from 73 to 31% 16 years after the development of overt nephropathy.

In accordance with the "Standards of Medical Care for Patients with Diabetes Mellitus," the position statement on "Treatment of Hypertension in Adults with Diabetes," and other recommendations, the primary goal of therapy for nonpregnant diabetic patients ≥18 years of age is to decrease blood pressure to and maintain it at <130 mmHg systolic and <80 mmHg diastolic. For patients with isolated systolic hypertension with a systolic pressure of ≥180 mmHg, the initial goal of treatment is to gradually lower the systolic blood pressure in stages. If initial goals are met and well tolerated, further lowering may be indicated.
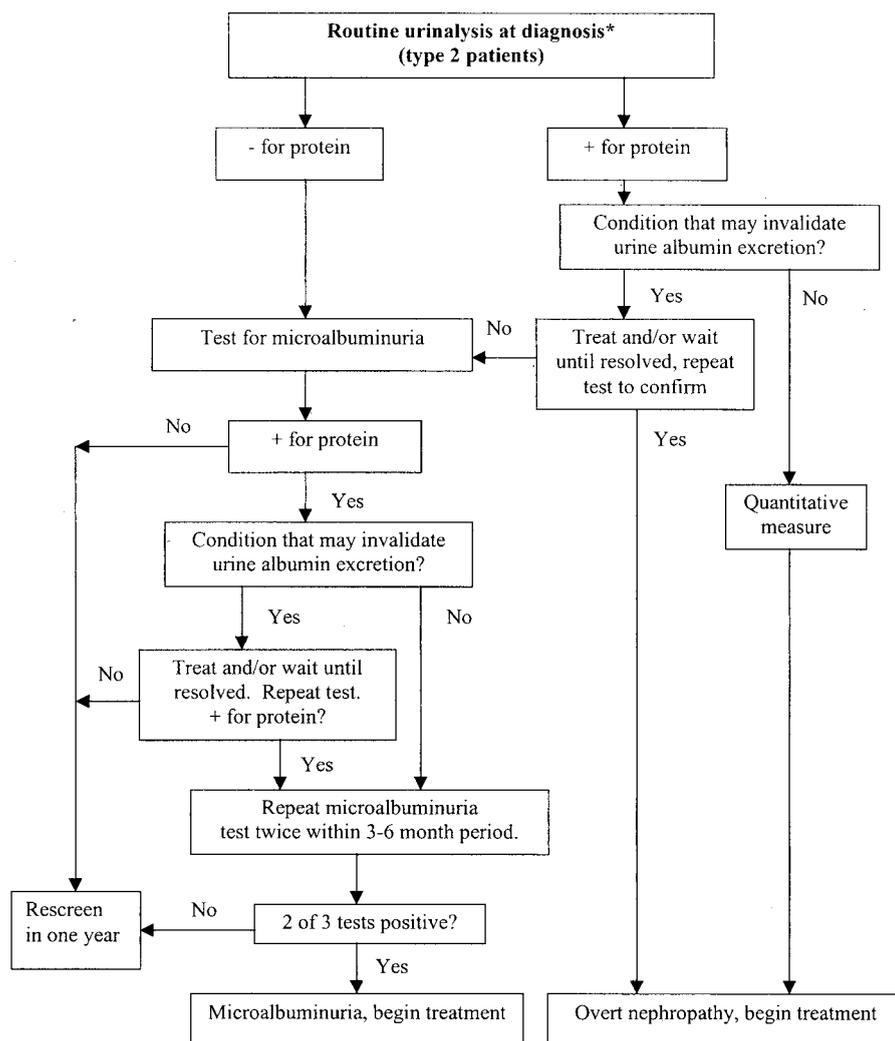
Figure 1—*Screening for microalbuminuria.*
*In type 1 diabetes, screening for microalbuminuria should begin after 5 years' disease duration.

A major aspect of initial treatment should consist of lifestyle modifications, such as weight loss, reduction of salt and alcohol intake, and exercise, as outlined in the "Standards of Medical Care for Patients with Diabetes Mellitus" and the position statement on "Treatment of Hypertension in Adults with Diabetes." In patients with underlying nephropathy, treatment with ACE inhibitors or ARBs is also indicated as part of initial therapy (see below). If after 4–6 weeks sufficient blood pressure reduction has not occurred, additional pharmacological therapy is indicated. (See the American Diabetes Association position statement "Treatment of Hypertension in Adults with Diabetes" for a complete discussion on this subject.) In general, these medica-

tions may be added in stepwise fashion and their individual use may depend on other factors such as fluid overload and vascular disease.

USE OF ANTIHYPERTENSIVE AGENTS

— The positive response to antihypertensive treatment coupled with the concept that often there is a progressive deterioration of renal function regardless of the underlying etiology gave rise to the idea that hemodynamic factors may be critical in furthering the fall in GFR. In this hypothesis, damage to glomeruli causes changes in the microcirculation that result in hyperfiltration occurring in the remaining glomeruli

with increased intra-glomerular pressure and increased sensitivity to angiotensin II; the single-nephron hyperfiltration with intraglomerular hypertension is itself damaging. Many studies have shown that in hypertensive patients with type 1 diabetes, ACE inhibitors can reduce the level of albuminuria and can reduce the rate of progression of renal disease to a greater degree than other antihypertensive agents that lower blood pressure by an equal amount. Other studies have shown that there is benefit in reducing the progression of microalbuminuria in normotensive patients with type 1 diabetes and normotensive and hypertensive patients with type 2 diabetes.

Use of ACE inhibitors or ARBs may exacerbate hyperkalemia in patients with advanced renal insufficiency and/or hyporeninemic hypoaldosteronism. In older patients with bilateral renal artery stenosis and in patients with advanced renal disease even without renal artery stenosis, ACE inhibitors may cause a rapid decline in renal function. Whether this occurs with ARBs is unknown. Cough may also occur with ACE inhibitors. ACE inhibitors are contraindicated in pregnancy and therefore should be used with caution in women of childbearing potential. There is no data on ARB use in pregnancy, but they are classified as class C/D.

Because of the high proportion of patients who progress from microalbuminuria to overt nephropathy and subsequently to ESRD, use of ACE inhibitors or ARBs is recommended for all patients with microalbuminuria or advanced stages of neuropathy. The effect of ACE inhibitors appears to be a class effect, so choice of agent may depend on cost and compliance issues.

The recent UKPDS compared antihypertensive treatment with an ACE inhibitor to that with a β-blocker. Both drugs were equally effective in lowering blood pressure and there were no significant differences in the incidence of microalbuminuria or proteinuria. However, because of the low prevalence of nephropathy in the population studied, it is unclear whether there were sufficient events to observe a protective effect of either drug on the progression of nephropathy. Some studies have demonstrated that the non-dihydropyridine calcium channel blocker (NDCCB) classes of calcium-channel blockers can reduce the level of albuminuria, but no studies to date have demonstrated a re-

duction in the rate of fall of GFR with their use.

PROTEIN RESTRICTION — Animal studies have shown that restriction of dietary protein intake also reduces hyperfiltration and intraglomerular pressure and retards the progression of several models of renal disease, including diabetic glomerulopathy: Several small studies in humans with diabetic nephropathy have shown that a prescribed protein-restricted diet of $0.6 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (subjects actually only achieved a restriction of $0.8 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) retards the rate of fall of GFR modestly. However, the Modified Diet in Renal Disease Study, in which only 3% of the patients had type 2 diabetes and none had type 1 diabetes, failed to show a clear benefit of protein restriction.

At this point in time, the general consensus is to prescribe a protein intake of approximately the adult Recommended Dietary Allowance (RDA) of $0.8 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ($\sim 10\%$ of daily calories) in the patient with overt nephropathy. However, it has been suggested that once the GFR begins to fall, further restriction to $0.6 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ may prove useful in slowing the decline of GFR in selected patients. On the other hand, nutrition deficiency may occur in some individuals and may be associated with muscle weakness. Protein-restricted meal plans should be designed by a registered dietitian familiar with all components of the dietary management of diabetes.

OTHER ASPECTS OF TREATMENT — Other standard modalities for the treatment of progressive renal disease and its complications (e.g., osteodystrophy) must also be used when indicated, such as sodium and phosphate restriction and use of phosphate binders. When the GFR begins to decline substantially, referral to a physician experienced in the care of such patients is indicated. Radiocontrast media are particularly nephrotoxic in patients with diabetic nephropathy, and azotemic patients should be carefully hydrated before receiving any procedures requiring contrast that cannot be avoided.

General recommendations
A-Level evidence
- To reduce the risk and/or slow the progression of nephropathy, optimize glucose control.

- To reduce the risk and/or slow the progression of nephropathy, optimize blood pressure control.

Screening
Expert consesus
- Perform an annual test for the presence of microalbuminia in *1*) type 1 diabetic patients who have had diabetes >5 years and *2*) all type 2 diabetic patients starting at diagnosis.

Treatment
A-Level evidence
- In the treatment of albuminuria/nephropathy both ACE inhibitors and ARBs can be used:
  - In hypertensive and nonhypertensive type 1 diabetic patients with microalbuminuria or clinical albuminuria, ACE inhibitors are the initial agents of choice;
  - In hypertensive type 2 diabetic patients wiht microalbuminuria or clinical albuminuria, ARBS are the initial agents of choice.

- If one class is not tolerated, the other should be substituted.

B-Level evidence
- With the onset of overt nephropathy, initiate protein restriction to $\leq 0.8 \, \text{g} \cdot \text{kg}^{-1}$ body wt $\cdot \text{day}^{-1}$ ($\sim 10\%$ of daily calories), the current adult recommended daily allowance for protein. Further restriction may be useful in slowing the decline of GFR in selected patients.

- Combination of ACE inhibitors and ARBs will decrease albuminuria more than use of either agent alone.

Expert consensus
- If ACE inhibitors or ARBs are used, monitor serum potassium levels for the development of hyperkalemia.

- Consider referral to a physician experienced in the care of diabetic renal disease when the GFR has fallen to either $<70 \, \text{ml} \cdot \text{min}^{-1} \cdot 173 \, \text{m}^{-2}$, serum creatinine has increased to $>2.0 \, \text{mg/dl}$ ($>180 \, \mu\text{mol/l}$), or difficulties occur in the management of hypertension or hyperkalemia.

- Consider the use of non-DCCBs in patients unable to tolerate ACE inhibitors or ARBs.

SUMMARY — Annual screening for microalbuminuria will allow the identification of patients with nephropathy at a point very early in its course. Improving glycemic control, aggressive antihypertensive treatment, and the use of ACE inhibitors or ARBs will slow the rate of progression of nephropathy. In addition, protein restriction and other treatment modalities such as phosphate lowering may have benefits in selected patients.

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