



# Clinical Evidence Handbook

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## Diabetic Nephropathy: Preventing Progression

MICHAEL SHLIPAK, *San Francisco Veterans Affairs Medical Center, San Francisco, California*

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Up to one-third of persons with type 1 or 2 diabetes mellitus will develop microalbuminuria or macroalbuminuria after 20 years. Smoking, poor glycemic control, male sex, older age, and ethnicity are also risk factors.

- Microalbuminuria can also be caused by hypertension, which often complicates type 2 diabetes and makes the diagnosis more difficult.

- Diabetic nephropathy increases the risk of end-stage renal disease (ESRD) and mortality, and is associated with increased cardiovascular risk.

In persons with type 1 diabetes, angiotensin-converting enzyme inhibitors reduce progression of early nephropathy, whereas in persons with late nephropathy, they reduce the risk of end-stage renal failure and death.

- Intensive glycemic control reduces progression of nephropathy compared with conventional control in persons with early renal disease, but we do not know whether glycemic control is effective in persons with late nephropathy.

We do not know whether angiotensin-II receptor blockers, dietary protein restriction, or tight control of blood pressure reduce the risks of renal or cardiovascular disease, or improve survival, in persons with early or late nephropathy.

In persons with type 2 diabetes, angiotensin-converting enzyme inhibitors reduce progression from early to late nephropathy and may reduce cardiovascular events, but we do not know whether they are beneficial in late nephropathy.

- Angiotensin-II receptor blockers may reduce progression of nephropathy in persons with early or late nephropathy.

- Lowering of diastolic blood pressure, even if not raised initially, reduces the risk of progression of early nephropathy, but we

do not know whether it is effective in late nephropathy.

- We do not know whether protein restriction or tight glycemic control are beneficial in early or late nephropathy.

### Definition

Diabetic nephropathy is a clinical syndrome in persons with diabetes, characterized by albuminuria on at least two occasions separated by three to six months. Diabetic nephropathy is usually accompanied by hypertension, progressive rise in proteinuria, and decline in renal function. In type 1 diabetes, five stages have been proposed. Of these, stages 1 and 2 are equivalent to preclinical nephropathy and are detected only by imaging or biopsy. Stage 3 is synonymous with early nephropathy—the clinical term used in this review. Stage 4 nephropathy is also known clinically as late nephropathy, and this term will be used for the remainder of this review. Stage 5 represents the progression to ESRD.

*Population:* For the purpose of this review, we have included persons with diabetes and early or late nephropathy. Early nephropathy presents as microalbuminuria, usually defined by an albuminuria level of 30 to 300 mg per day (or urine albumin-to-creatinine ratio of 30 to 300 mg per g [3.4 to 34.0 mg per mmol]). Late nephropathy presents as macroalbuminuria, characterized by an albuminuria level greater than 300 mg per day (or urine albumin-to-creatinine ratio greater than 300 mg per g). The treatment of persons with diabetes and ESRD is not covered in this review.

### Incidence and Prevalence

After 20 years of having type 1 or 2 diabetes, the cumulative risk of proteinuria is 27 to 28 percent, and the overall prevalence of microalbuminuria and macroalbuminuria is 30 to

## Clinical Questions

### What are the effects of treatments to prevent progression of nephropathy in persons with type 1 diabetes mellitus and early nephropathy?

Beneficial	ACE inhibitors (reduce progression to late nephropathy)
	Intensive glycemic control (reduces progression to late nephropathy)
Unknown effectiveness	ARBs
	Protein restriction
	Tight control of blood pressure

### What are the effects of treatments to prevent progression of nephropathy in persons with type 1 diabetes and late nephropathy?

Beneficial	Captopril
Unknown effectiveness	ARBs
	Glycemic control
	Protein restriction
	Tight control of blood pressure

### What are the effects of treatments to prevent progression of nephropathy in persons with type 2 diabetes and early nephropathy?

Beneficial	ACE inhibitors
	ARBs
	Tight control of blood pressure
Unknown effectiveness	Glycemic control
	Protein restriction

### What are the effects of treatments to prevent progression of nephropathy in persons with type 2 diabetes and late nephropathy?

Beneficial	ARBs
Unknown effectiveness	ACE inhibitors
	Glycemic control
	Protein restriction
	Tight control of blood pressure

ACE = angiotensin-converting enzyme; ARB = angiotensin-II receptor blocker.

35 percent. In addition, the incidence of diabetic nephropathy is increasing, partly due to the growing epidemic of type 2 diabetes, and because of increased life expectancies. For example, the incidence in the United States has increased by 150 percent in the past decade.

## Etiology and Risk Factors

Duration of diabetes, older age, male sex, smoking, and poor glycemic control have all been found to be risk factors in the development of nephropathy. In addition, certain ethnic groups seem at greater risk (see Prognosis). Microalbuminuria is less pathognomonic of nephropathy among persons with type 2 diabetes because hypertension, which is a common complication of type 2 diabetes, can also cause microalbuminuria. Hypertension can also cause

renal insufficiency; therefore, the time to development of renal insufficiency can be shorter in type 2 diabetes than in type 1. Renal biopsy may be advisable in persons who have an atypical course. In addition, there are some differences in the progression of type 1 and type 2 diabetic nephropathy. In persons with type 2 diabetes, albuminuria is more often present at diagnosis. Hypertension is also more common in type 2 diabetic nephropathy. Finally, microalbuminuria is less predictive of late nephropathy in persons with type 2 diabetes compared with type 1.

## Prognosis

Persons with microalbuminuria are at increased risk of progression to macroalbuminuria and ESRD. The natural history of diabetic nephropathy is better defined in type 1 than type 2 diabetes. In type 2 diabetes, the course can be more difficult to predict, primarily because the date of onset of diabetes is less commonly known, and comorbid conditions can contribute to renal disease. Without specific interventions, about 80 percent of persons with type 1 diabetes, and 20 to 40 percent of persons with type 2 diabetes and microalbuminuria, will progress to macroalbuminuria.

Diabetic nephropathy is associated with poor outcomes. In the United States, diabetes accounts for 48 percent of all new cases of ESRD. In the United Kingdom, it is the most common cause of ESRD, accounting for 20 percent of cases. Persons with type 1 diabetes and proteinuria have been found to have a 40-fold greater risk of mortality than persons without proteinuria. The prognostic significance of proteinuria is less extreme in type 2 diabetes, although persons with proteinuria have a fourfold risk of death compared with persons without proteinuria. In addition, increased cardiovascular risk has been associated with albuminuria in persons with diabetes. African American, Native American, and Mexican American persons have a much higher risk of developing ESRD in the setting of diabetes compared with white persons. In the United States, African American persons with diabetes progress to ESRD at a much more rapid rate than white persons with diabetes. In England, the rates for initiating treatment for ESRD are 4.2 times higher for African Caribbean persons and 3.7 times higher for Indo-Asian persons than for white persons. Native American persons of the Pima tribe in the southwestern United States have much higher rates of diabetic nephropathy than white persons, and also progress to ESRD at a faster rate.

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