Diabetic nephropathy

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Abstract

Diabetic nephropathy is a major underlying cause of morbidity and mortality in both type 1 and type 2 diabetes mellitus, giving rise principally to cardiovascular disease, in particular heart failure, the incidence of which is about 15-fold greater in patients with diabetic kidney disease. The all-cause mortality in patients with diabetic nephropathy is nearly 20–40 times higher than in patients without nephropathy. Many patients with diabetes, in particular type 2 diabetes, and renal impairment die from cardiovascular disease well before they progress to end-stage renal disease. Nevertheless, diabetic nephropathy is the most common cause of end-stage renal disease worldwide. Suboptimal glycaemic control and a higher blood pressure are particularly important risk factors for the development of diabetic nephropathy. Over a lifetime, diabetic nephropathy occurs in approximately 30–35% of patients with type 1 and type 2 diabetes. The disease can be detected in most cases many years before the development of advanced renal failure through the detection of raised urinary albumin excretion – microalbuminuria. Early detection allows time for the intensive treatment of glycaemic control, blood pressure and other cardiovascular risk factors, such as lipids, in order to reduce the morbidity and mortality.

Keywords diabetic nephropathy; end-stage renal failure; glycaemic control; microalbuminuria

Definition and detection

By convention, diabetic nephropathy is defined as the appearance of persistent 'clinical' albuminuria (albumin excretion rate (AER) >300 mg/24 hours) in an individual with diabetes mellitus for more than 5 years and concomitant retinopathy, in the absence of urinary tract infection (UTI), other renal diseases or heart failure. This process is often associated with increasing blood pressure. After initial stabilization of metabolic control, all patients should be screened for albuminuria at least once per year. Screening for diabetic nephropathy is usually performed by measuring the albumin:creatinine ratio (ACR) in a single early-morning urine sample. Values of 2.5 mg/mmol or more in men, or 3.5 mg/mmol or more in women are abnormal. An elevated ACR should be confirmed before the diagnosis of nephropathy is established.

Epidemiology

In type 1 diabetes, the most common cause of kidney damage is classical diabetic nephropathy. Kidney disease is relatively rare in the first 5–10 years, but the incidence increases rapidly over the next 10 years, to a peak of about 3% per year after 15 years. It then declines to about 1% per year in patients with type 1 diabetes of 40 years' duration or more. Those with diabetes for more than 35 years who have not yet developed kidney disease are at low risk of doing so. This pattern suggests that only some patients are susceptible to renal disease in diabetes, and provides strong evidence that genetic susceptibility combined with the cumulative effect of hyperglycaemia is necessary. A family history of diabetic kidney disease, or indeed a parental history of cardiovascular disease or hypertension, increases the risk of diabetic kidney disease in the individual with type 1 diabetes.

In type 2 diabetes, classical diabetic kidney disease also occurs, but in an older population other kidney diseases, particularly hypertensive ischaemic damage, are more common and kidney disease in those with type 2 diabetes may have atypical features.

Classical diabetic kidney disease in type 2 diabetes often occurs in younger individuals, and may be accompanied by retinopathy and progression from microalbuminuria to overt proteinuria.

In older individuals with type 2 diabetes, retinopathy and proteinuria may be absent or minimal. Although other renal diseases should be considered and excluded, the kidney lesion is often related to hypertension or glomerular ischaemia and its treatment is largely the same.

The cumulative risk of nephropathy in type 2 diabetes varies with ethnic origin, ranging from 25% in those of European origin to about 50% in other ethnic groups (e.g. Afro-Caribbeans, Asian-Indians, Japanese). Those of African, Caribbean or Asian-Indian origin may develop type 2 diabetes more commonly and at a younger age.

Type 2 diabetes is more common than type 1, and in some areas the number of patients with type 2 diabetes requiring renal replacement therapy (dialysis or transplantation) exceeds that in type 1. Worsening glycaemic control, higher blood pressure, smoking and adverse lipid profile are all risk factors for diabetic nephropathy in both type 1 and type 2 diseases.

Clinical course

Diabetic nephropathy is a multi-stage condition that takes several years to become clinically overt (Figure 1). At the onset of diabetes, there are usually changes in renal function, such as glomerular hyperfiltration, increased renal blood flow and hypertrophy of the kidney. Most of these changes can be reversed at an early stage by good glycaemic control, but in many patients they persist and may be important in the later development of clinical nephropathy.

Microalbuminuria

In the past, the definition of diabetic nephropathy was dictated by the lower limit of detection of available urinary albumin assays. Development of more sensitive assays enabled detection of previously undetectable sub-clinical increases in urinary albumin excretion, which were termed 'microalbuminuria'. This is the first indication of diabetic nephropathy, and is defined as a persistent increase (in at least two of three consecutive, urine specimens) in AER to 20–200 μg/minute (30–300 mg/day). It may be detected 1 year after the onset of diabetes in post-pubertal patients with type 1 disease, and at diagnosis in type 2. There is significant structural glomerular disease even at this early phase, and the glomerular filtration rate (GFR) starts to

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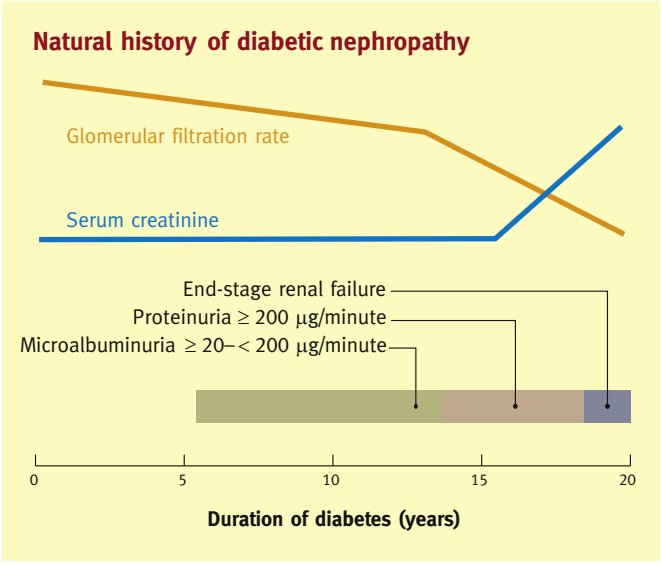
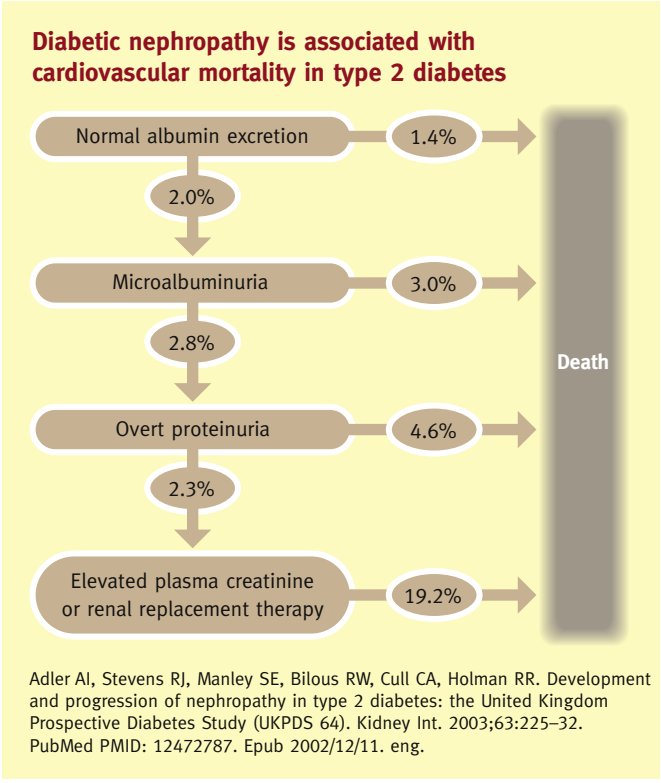


Figure 1



Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63:225–32. PubMed PMID: 12472787. Epub 2002/12/11. eng.

Figure 2

decline during the phase of microalbuminuria, though it may remain within the normal range until the AER approaches 200 μg/minute (300 mg/day). In healthy adults the normal AER ranges between 1.5 and 20 μg/minute with a median value around 6.5 μg/minute. ACR correlates closely with AER and the relative constancy of urine creatinine excretion corrects to an extent for variability of urine albumin.[1]

Long-term studies in type 1 diabetes have demonstrated that microalbuminuria is associated with a 20-fold risk of progression to overt renal disease compared with normoalbuminuria.[1–3]

Without intervention, microalbuminuria progresses to clinical albuminuria over approximately 10–15 years. In studies that followed patients from the late 1960s to early 1980s, approximately 80% of patients with type 1 diabetes and microalbuminuria developed persistent clinical albuminuria. However, more recent studies suggest that the natural history has become more variable: in around 20% microalbuminuria progresses towards clinical albuminuria over 5–9 years, whereas in 50% it remains in the microalbuminuric range, and in approximately 30% of patients AER reverts back towards the normal range (<30 μg/minute).[1] This change most likely reflects advances and improvements in medical care with ever more stringent glycaemic, lipid and blood pressure control as well as the widespread use in recent years of agents such as ACE inhibitors and angiotensin II receptor blockers (ARB). Microalbuminuria is also strongly predictive of death from cardiovascular disease, particularly in older patients with type 2 diabetes (Figure 2). Furthermore, in those with type 1 diabetes who develop microalbuminuria after a very long duration of disease, it is a more consistent predictor of cardiovascular than of progressive renal disease.

Microalbuminuria is also associated with retinopathy, peripheral vascular disease and neuropathy.

In type 1 diabetes, blood pressure increases in patients with microalbuminuria (Figure 3), and lipid abnormalities, including increased low-density lipoprotein cholesterol (LDL-C), total triglycerides and apolipoprotein B, and reduced high-density lipoprotein (subclass 2) cholesterol, develop. These progressive abnormalities are seen in both type 1 and type 2 diabetes, though in the latter they often occur on a background of pre-existing hypertension and dyslipidaemia. Microalbuminuria is also associated with generalized endothelial dysfunction in both type 1 and type 2 diabetes.

Persistent albuminuria

An increase in AER to a persistent value of more than 200 μg/minute (>300 mg/day) marks the onset of clinically defined 'overt diabetic nephropathy' and is a harbinger of renal failure and cardiovascular complications in both types of diabetes. Blood pressure rises progressively in this phase in both type 1 and type 2 diabetes.

Over time, the protein loss may increase to more than 3–4 g/day and occasionally lead to nephrotic syndrome with hypoalbuminaemia, hypercholesterolaemia and peripheral oedema. As proteinuria rises, the urine protein:creatinine ratio (PCR) is measured in preference to the ACR as the proteinuria becomes less selective. The heavier the proteinuria, particularly if this exceeds 2–3 g/day, the more rapid is the loss of GFR. Lipid disturbances and atherosclerotic complications are prominent in this phase. In those patients who develop persistent clinical albuminuria, GFR gradually declines in a linear fashion; the rate of decline (average 4.5 ml/minute/year) is variable and depends on how well promoters of progression, such as hypertension and degree of albuminuria, are controlled, and on individual response to treatment. Although the rate fall in GFR varies from patient to patient, it remains relatively constant for each individual patient. Since the advent of early and intensive treatment of hypertension, the time from the onset of clinical albuminuria to death has virtually trebled from 7 to 21 years.[1]