Diabetic kidney disease (DKD) is the single commonest cause of end-stage renal failure worldwide.

The onset of clinically overt DKD is defined as persistent proteinuria: that is, a urinary protein excretion of 0.5 g/day or more in the presence of retinopathy, elevated blood pressure (BP) and declining glomerular function, but in the absence of urinary tract infection, other renal disease or heart failure. This definition was mainly dictated by the lower limit of detection of urinary albumin. Urinary albumin excretion was measured in timed urine collections, from which was derived an albumin excretion rate (AER), either overnight or over 24 hours.

The development of sensitive assays for urinary albumin allowed the detection of subclinical rises in urinary albumin excretion, termed ‘microalbuminuria’. Early studies of urinary albumin excretion used different cut-off points for the definition of microalbuminuria. A consensus meeting in 1986 defined microalbuminuria as an AER of 20–200 µg/min (30–300 mg/day), based upon sensitivity, specificity and predictive value for DKD in type 1 diabetes. This definition is largely accepted also in type 2 diabetes, although some workers argue for a lower boundary for microalbuminuria of 10 µg/min, based upon epidemiological studies showing that increases above this level are predictive of cardiovascular disease (CVD) in type 2 diabetes.

Approximately 80% of type 1 diabetes patients who develop microalbuminuria within 15 years of the onset of diabetes progress to DKD. The natural history of the condition in type 1 diabetes is illustrated in Fig 1.

Proteinuria and the kidney in diabetes

Rather than merely predicting DKD, microalbuminuria is associated with significant renal lesions. In both type 1 and type 2 diabetes there are significantly more glomerular lesions in patients with microalbuminuria than in those with normoalbuminuria. In type 2 diabetes the lesions may be more heterogeneous and non-diabetic renal diseases more frequent, particularly in patients without retinopathy. At the stage of microalbuminuria, the glomerular filtration rate (GFR) is usually well maintained.

The development of persistent macroalbuminuria is followed by a progressive variable decline in the GFR. The AER is related to disease progression, and a reduction in AER in response to treatment predicts a reduction in the rate of GFR loss.

Proteinuria and cardiovascular disease in diabetes

Micro- and macroalbuminuria are markers of generalised vascular disease, with evidence of endothelial dysfunction and, in particular, with an increased risk of CVD. This particularly applies to the older Caucasian population with type 2 diabetes in whom microand macroalbuminuria are associated with other cardiovascular risk factors. In type 1 diabetes, patients with macroalbuminuria have a relative mortality rate from CVD 37 times higher than the non-diabetic population and about 10 times higher than those with diabetes without macroalbuminuria. Thus, CVD is the commonest cause of death for patients with either type 1 or type 2 diabetes who develop microalbuminuria or overt DKD.

Associations of proteinuria in diabetes

Blood pressure

In the late 1960s a significant correlation was found between AER and both systolic and diastolic BP in a population with type 2 diabetes. In type 1 diabetes, AER and BP increase in parallel in those who develop microalbuminuria.
Interestingly, patients who maintain a mean arterial pressure below 90 mmHg (120/75 mmHg) are at very low risk of developing microalbuminuria. In type 2 diabetes, higher BPs are associated with a greater risk of developing microalbuminuria. In the UK Prospective Diabetes Study (UKPDS), intensive BP treatment and tight BP control (mean 144/82 mmHg) resulted in a 29% reduction in the risk of microalbuminuria after six years, as compared with less tight BP control (mean 154/87 mmHg). Systolic and diastolic BP rise during both micro- and macroalbuminuria in type 1 and type 2 diabetes, whether measured as single clinic or 24-hour recordings. This has led to considerable redefinition of hypertension in diabetes.

Lipid disturbances

Both micro- and macroalbuminuria are associated with an unfavourable lipid profile, with higher concentrations of total plasma cholesterol, very low-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and with an increase in atherogenic small dense LDL particles and reduced high-density lipoprotein (HDL) levels. A significant portion of the excess cardiovascular risk associated with microalbuminuria has been ascribed to changes in lipids, particularly in type 2 diabetes.

Management

Blood pressure

Treating the raised BP is paramount, but the BP targets and which agents should be used are still a matter of some debate. In type 1 diabetes, angiotensin converting enzyme (ACE) inhibitors are considered first-line treatment in patients with micro- or macroalbuminuria. A recent meta-analysis of clinical trials of ACE inhibitors in patients with type 1 diabetes and microalbuminuria found that this therapy reduced progression to macroalbuminuria by 79%, with regression to normoalbuminuria occurring 2.6 times more often than with other antihypertensive agents. Captopril halved the risk of a doubling of the serum creatinine over a median three-year follow-up. This was also associated with a 50% risk reduction in a combined end-point of death or renal replacement therapy compared with a control group in which non-ACE inhibitors were used to maintain roughly the same BP. There is more controversy in type 2 diabetes. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial showed a significant reduction after five years in the number of myocardial infarctions (MI) in a group treated with enalapril as compared to patients treated with nisoldipine. The number of events was small, and the difference appears to be due to a beneficial effect of ACE inhibitors rather than to a detrimental effect of calcium antagonists.

Table 1. Higher arterial pressures are associated with faster progression of renal disease (GFR = glomerular filtration rate).

<table>
<thead>
<tr>
<th>Mean arterial pressure (mmHg)</th>
<th>Rate of fall of GFR (mls/min/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;91</td>
<td>3.9</td>
</tr>
<tr>
<td>91–106</td>
<td>4.4</td>
</tr>
<tr>
<td>&gt;106</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Cohort study of rate of fall of GFR in type 1 diabetes

Recently, the MICRO-HOPE substudy of the Heart Outcomes Prevention Evaluation (HOPE) study showed that ramipril, compared with placebo, lowered the risk both of overt nephropathy and of a primary combined end-point of MI, stroke or CVD death in all patients with diabetes, including those with microalbuminuria. However, the Hypertension in Diabetes Study showed equivalent efficacy for ACE inhibitors and β-blockers in the prevention of micro- and macrovascular disease. The Joint National Committee on Detection, Evaluation and Treatment of Hypertension recommends target sitting BPs as follows:

- below 130/85 mmHg for all patients with diabetes
- below 125/75 mmHg for renal protection in those with DKD since there is ample evidence that tight BP control slows the decline of GFR (Table 1).
There are also suggestions that antihypertensive therapy, in particular ACE inhibitor therapy, should be titrated to achieve the maximum antiproteinuric effect.

Physicians should be aware of the risks of postural hypotension when BP is treated aggressively. Caution is also required in patients with type 2 diabetes, particularly those with peripheral vascular disease (who have a higher prevalence of renovascular disease) in whom ACE inhibitors can cause renal impairment and hypotension.

The clear message is the importance of BP control; this will often require more than one agent. Current data support the use of ACE inhibitors as first-line therapy, particularly in type 1 and perhaps also in type 2 diabetes.

Glycaemic control
The importance of glycaemic control in the primary prevention of micro- and macroalbuminuria is established. The benefit of improved glycaemic control in the progression of microalbuminuria and DKD is controversial, with several small and conflicting intervention studies. In prospective studies, better glycaemic control is associated with a slower renal progression if the BP is well controlled. Good glycaemic control is of course important for the treatment of other diabetic micro- and macrovascular complications. Strict glycaemic control becomes more difficult as renal function falls with a fall in insulin requirement, and there is a greater risk of hypoglycaemia in renal failure.

Lipid lowering treatment
Higher cholesterol levels are associated with faster progression of renal disease. Although there is no firm evidence that lipid lowering therapy alters the rate of progression of renal disease, the strong association with CVD suggests that lipid lowering should be considered, particularly in people with micro- and macroalbuminuria. The recent Joint British Recommendations on Prevention of Coronary Heart Disease in Clinical Practice advocate treatment of those with diabetes and a serum cholesterol/HDL cholesterol ratio above 5.5, whose 10-year coronary heart disease risk is 15% or greater, as in those with micro- or macroalbuminuria.

Dietary treatment
Dietary treatment remains controversial, although the St Vincent guidelines for type 1 diabetes recommend that it is reasonable in patients with DKD to limit the protein intake to 0.8–1 g/kg body weight per day. Close monitoring is necessary when prescribing low protein diets.

Smoking
Smoking is related to both the development and the progression of microalbuminuria and DKD. In addition, the strong association with CVD means that smoking should be particularly discouraged in patients with micro- and macroalbuminuria.

Urinary tract infection
Urinary tract infection is commoner in diabetes. As it can precipitate a decline in renal function, a rapid increase in protein leak should provoke the sending of an MSU for culture and sensitivity.

Screening for microalbuminuria in diabetes
Intensive treatment of those with microalbuminuria and DKD can considerably slow or even stabilise progression of the disease, so screening is mandatory in the care of the patient with diabetes. Routine screening for microalbuminuria is feasible, and several different methods are available (Table 2). Measurement of the albumin/creatinine ratio in an early morning urine specimen is convenient, and sensitive dipsticks are now commercially available. The gold standard, however, remains the formal measurement of AER; clear instructions to the patient are necessary to ensure a valid collection. The diagnosis of microalbuminuria should be confirmed more than once, preferably on three occasions over a six-week period, as there is significant day-to-day variation.

References


The ACE Inhibitors in Diabetic Nephropathy Trialist Group E. When should ACE Inhibitors be used in IDDM? A combined analysis of clinical trials. *Diabetologia* 1997;41(Suppl 1): abstract.


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