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. It is strongly associated with cardiovascular disease, particularly heart failure, the incidence of which is about 15-fold greater in patients with diabetic nephropathy. 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 single 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 usually be detected many years before the development of advanced renal failure through the detection of raised urinary albumin excretion. Early detection allows time for the intensive treatment of glycaemic control, blood pressure and other cardiovascular risk factors, such as lipids, to reduce the morbidity and mortality.

Keywords Diabetic nephropathy; end-stage renal failure; glycaemic control; microalbuminuria; MRCP

Key points

- Diabetic nephropathy is characterized by abnormal urinary protein excretion with rising blood pressure and other microvascular complications (usually retinopathy), and is associated with much higher cardiovascular risk
- Above-target glycaemic control, rising blood pressure, smoking, higher low-density lipoprotein-cholesterol and triglycerides, and family history of kidney/cardiovascular disease all increase the risk of diabetic nephropathy
- Antidiabetic agents should be used with particular care in patients with reduced renal function
- Multifactorial interventions delay the onset and progression of kidney disease

Definition and detection

Historically, diabetic nephropathy has been defined as the appearance of persistent 'clinical' albuminuria (albumin excretion rate (AER) >300 mg/24 hours) in an individual with diabetes mellitus for >5 years and concomitant retinopathy, in the absence of urinary tract infection, other renal diseases or heart failure.[1] This is often associated with increasing blood pressure. This level of proteinuria was chosen as it was reliably detected using the tests of the day. Nowadays we can detect urinary albumin at much lower concentrations so can detect an earlier phase of kidney damage, which has come to be known as microalbuminuria.

Microalbuminuria is the first indication of diabetic nephropathy; it is defined as a persistent increase (in at least two of three consecutive urine specimens) in urinary albumin excretion. It is typically measured in early morning urine samples, and the urinary albumin concentration is expressed as the ratio to urinary creatinine to adjust for urinary concentration (albumin:creatinine ratio (ACR)). ACR values of 2.5 mg/mmol or more in men, or 3.5 mg/mmol or more in women, are abnormal as is an AER to 20–200 micrograms/minute (30–300 mg/day) in timed collections.[1,2]

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 ACR in a single early morning urine sample. An elevated ACR should be confirmed before a diagnosis of nephropathy is established.[1]

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.[1] It then declines to about 1% per year in patients with type 1 diabetes of 40 years' duration or more.[1] Individuals who have had diabetes for >35 years but 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.[1] A family history of diabetic kidney disease, or a parental history of cardiovascular disease or hypertension, increases the risk of diabetic kidney disease in individuals with type 1 diabetes.[1]

In type 2 diabetes, classical diabetic kidney disease also occurs; however, other kidney diseases, particularly hypertensive ischaemic damage, may occur particularly in an older population, and kidney disease in those with type 2 diabetes can have atypical features.[1,2] Classical diabetic kidney disease in type 2 diabetes often occurs in younger individuals, and is usually accompanied by retinopathy and the typical progression from microalbuminuria to overt proteinuria.[1]

In older individuals with type 2 diabetes, retinopathy and proteinuria can be absent or minimal. Although other renal

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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 individuals of European origin to about 50% in other ethnic groups (e.g. African-Caribbean, Asian-Indian, and Japanese).[1] Those of African, Caribbean or Asian-Indian origin develop type 2 diabetes more commonly and often at a younger age, which is associated with enhanced risk of nephropathy and cardiovascular disease. Worsening glycaemic control, higher blood pressure, smoking and adverse lipid profiles are all risk factors for diabetic nephropathy in both type 1 and type 2 diabetes.[1–3]

Clinical course

Diabetic nephropathy is a multistage 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 can be reversed at an early stage by good glycaemic control, but in many patients they persist and can be important in the later development of clinical nephropathy.[1,2]

Microalbuminuria

This may be detected 1 year after the onset of diabetes in postpubertal patients with type 1 diabetes, 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 decline during the phase of microalbuminuria, although it can remain within the normal range until the AER approaches 200 micrograms/minute (300 mg/day). In healthy adults, the normal AER ranges between 1.5 and 20 micrograms/minute, with a median value around 6.5 micrograms/minute. ACR correlates closely with AER, and the relative constancy of urine creatinine excretion corrects to an extent for variability of urine albumin.[1]

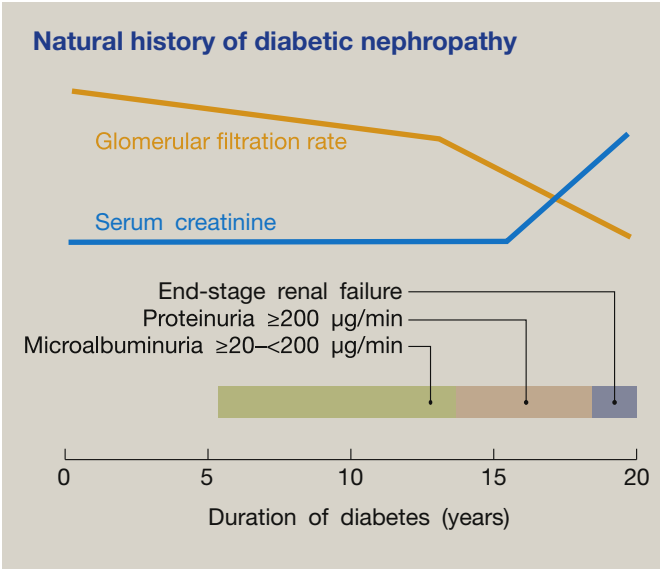

Figure 1

Without intervention, microalbuminuria progresses to greater levels of albuminuria/proteinuria over approximately 10–15 years. Glomerular filtration may be falling all this time, although it does not usually appear abnormal until the proteinuria is at a higher level. In studies that followed patients from the late 1960s to early 1980s, approximately 80% of those with type 1 diabetes and microalbuminuria developed persistent high-level albuminuria/proteinuria. Recent studies suggest that the prognosis may have improved, with progression of the kidney disease being less likely, so around 20% of microalbuminuria progresses towards clinical albuminuria over 5–9 years.[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 angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Diabetic nephropathy even at the stage of microalbuminuria is strongly predictive of death from cardiovascular disease, particularly in older patients with type 2 diabetes (Figure 2). Microalbuminuria is also associated with retinopathy, peripheral vascular disease and neuropathy.[1–3]

Blood pressure increases in patients with microalbuminuria (Figure 3), and lipid abnormalities develop; these include increased low-density lipoprotein (LDL)-cholesterol, total triglycerides (triacylglycerols) and apolipoprotein B, and reduced high-density lipoprotein (subclass 2)-cholesterol. These progressive abnormalities are seen in both type 1 and type 2 diabetes.[1–3] Microalbuminuria is also associated with generalized endothelial dysfunction.[1]

Persistent albuminuria

An increase in AER to a persistent value >200 micrograms/minute (>300 mg/day) marks the onset of historically 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. Stabilization of kidney function can be harder to achieve in this stage, and therefore easy detection and ‘aggressive’ treatment at an early stage is warranted.

Over time, the protein loss can increase to >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 >2–3 g/day, the more rapid the fall in GFR. Lipid disturbances and atherosclerotic complications are prominent in this phase.

In patients who develop persistent clinical albuminuria, GFR gradually declines in a linear fashion; the rate of decline (average 4.5 ml/minute per year) is variable and depends on how well promoters of progression, such as hypertension and degree of albuminuria, are controlled, and on the individual response to treatment. Although the rate of decline in GFR varies from patient to patient, it remains relatively constant for each individual patient. Since the advent of early and intensive treatment of blood pressure and other risk factors, the ‘median time’ from the onset of clinical albuminuria to death has virtually trebled, from 7 years to 21 years.[1]

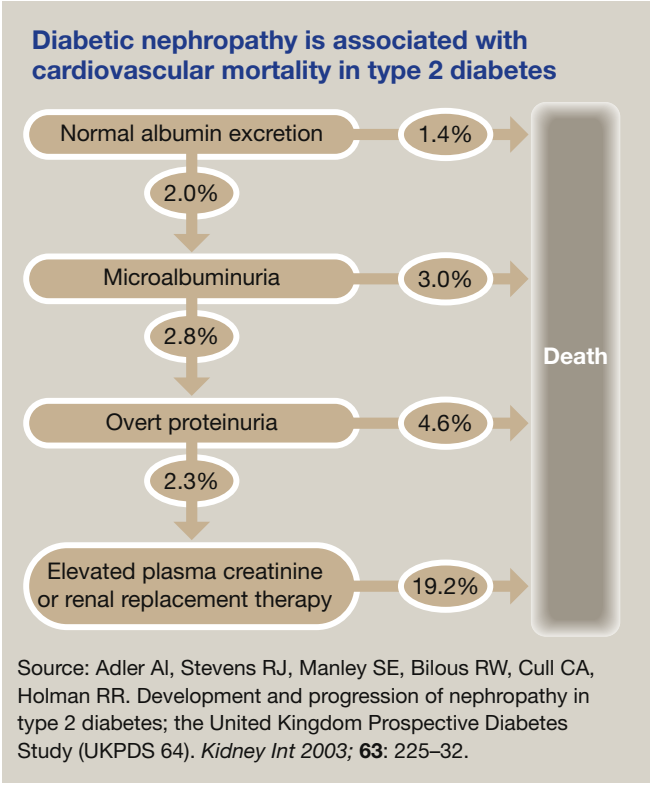

Figure 2

Diabetic retinopathy

Diabetic retinopathy usually accompanies persistent proteinuria, and its absence should alert health professionals to the possibility of a non-diabetic cause of the proteinuria. Features suggestive of non-diabetic kidney disease include absence of retinopathy, short duration (<5 years) of diabetes, rapid progression of renal dysfunction (fall in eGFR >15 ml/minute per year), onset of proteinuria without a history of microalbuminuria, haematuria and systemic features of other diseases e.g. vasculitis.[1,4]

Diagnosis

Normal values are:

- urinary albumin concentration <20 mg/litre
- ACR <2.5 mg/mmol in men, and <3.5 mg/mmol in women
- AER <20 micrograms/minute (<30 mg/day)
- eGFR often >90 ml/minute and always >60 ml/minute.

Screening tests (Figure 4)

ACR, blood pressure and estimated GFR (eGFR) should be measured at least once per year in all patients >12 years of age with diabetes.[2] Measurement of ACR is a reliable screening method, ideally performed on an early morning urine sample. It should be remembered that heavy exercise, urinary tract infection, acute illness or cardiac failure can transiently increase ACR and AER.[1]

Regrettably measurement of the ACR is the least likely to be performed of the recommended annual checks for people with diabetes which means a major opportunity for early intervention is lost.

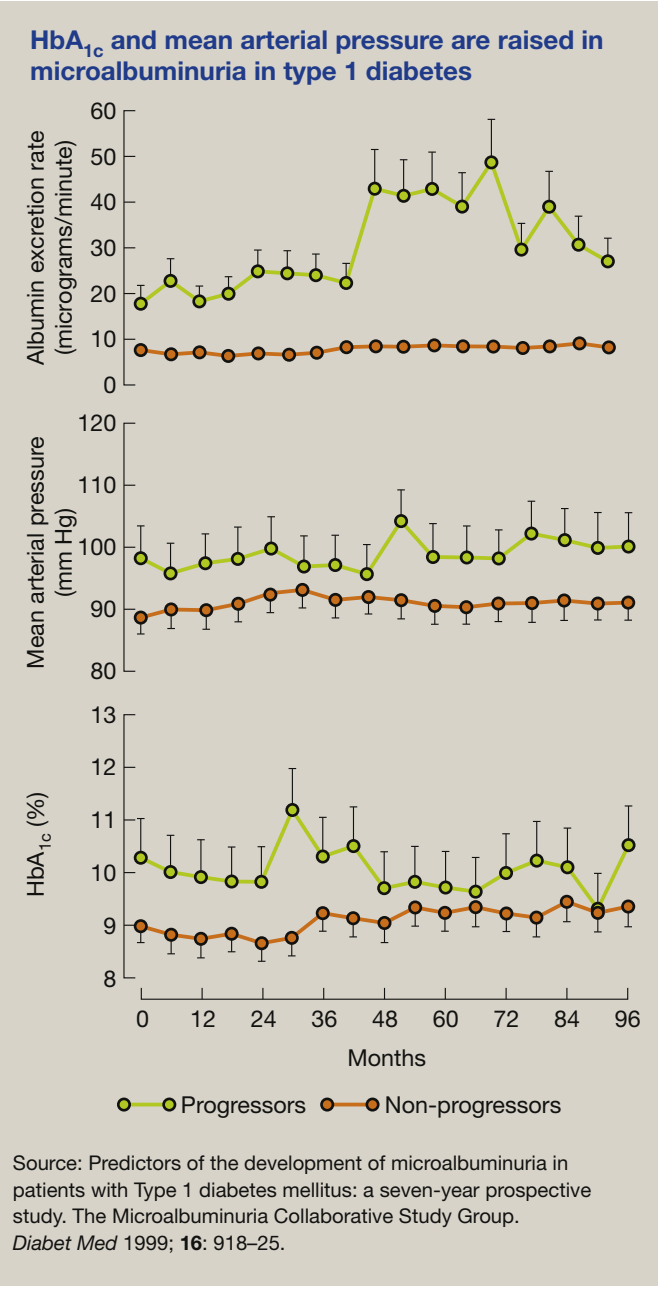

Figure 3

Confirmation

If ACR is raised, the test should be repeated. Confirmation in two of three urine samples tested within 6–12 weeks establishes the presence of microalbuminuria and kidney disease. The kidney disease can be staged using eGFR (>90 ml/minute is stage 1; 60–90 ml/minute in stage 2). If the eGFR already confirms stage 3 kidney disease (eGFR <60 ml/minute), the presence of microalbuminuria or proteinuria has prognostic significance, indicating a higher risk of renal progression and cardiovascular disease.[1–3]

Progression of the albuminuria should be checked, usually by repeated measurements of ACR or, as proteinuria rises and becomes less selective, PCR in an early morning urine sample. At higher levels of proteinuria, timed collections are occasionally

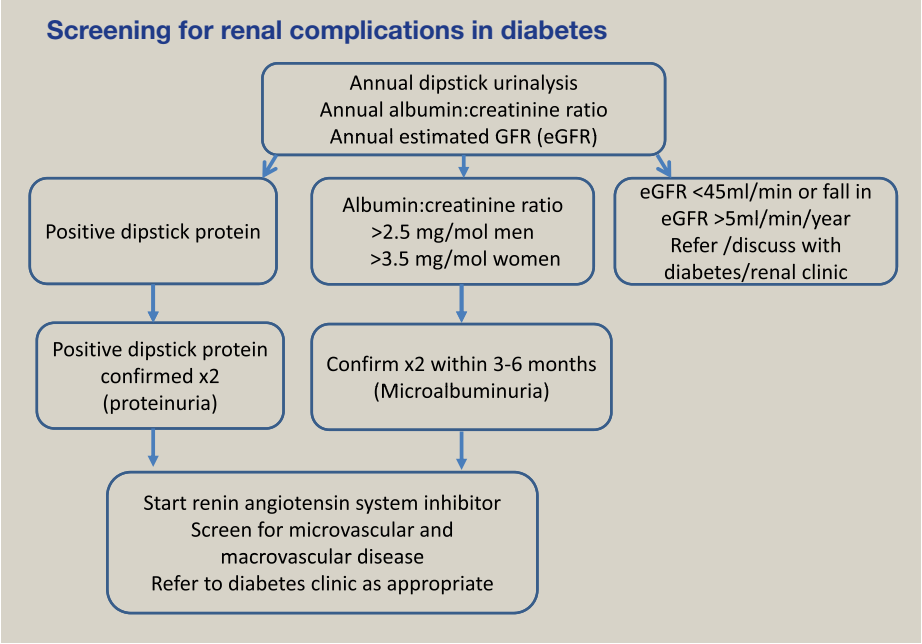

Figure 4

performed as the greater the degree of albuminuria, the higher the renal and cardiovascular risk.

In these patients, regular and more frequent check-ups should be undertaken to assess blood pressure, glycaemic control, serum lipids and serum creatinine or eGFR.[1–3]

Management

Glycaemic control

Good glycaemic control can prevent diabetic nephropathy in both type 1 and type 2 diabetes, and there is evidence that, once microalbuminuria has developed, good glycaemic control slows the progression of the kidney lesions.[1–3]

In diabetes, improved blood glucose control and intensified insulin treatment reduce histological worsening of glomerulopathy in individuals with microalbuminuria, and worse glycaemic control is associated with a faster decline in GFR.

Once renal function is impaired, renally excreted sulfonylureas, such as glibenclamide, glipizide and glimepiride, must not be used. Gliptins that are renally excreted require dose reduction when GFR falls <60 ml/minute.

Guidelines for metformin use vary internationally.[2–4] In advanced renal failure, metformin carries the risk of potentially life-threatening lactic acidosis. Nowadays, this usually happens in the context of acute kidney injury in a patient with chronic kidney disease. The risk–benefit ratio of using the drug should be considered carefully in all those with an eGFR <45 ml/minute, particularly if there is a previous history of acute kidney injury. When the risk has been assessed, metformin can be continued provided eGFR does not fall <30 ml/minute. It is important to consider temporary discontinuation of the drug in patients with symptoms such as nausea and diarrhoea or vomiting, which can lead to dehydration and an increased risk of acute kidney injury. It is important that patients are alerted to the risks of metformin during acute illness, particularly diarrhoea and vomiting, especially if there is already a low GFR.

A new class of drug – sodium glucose cotransporter (SGLT)-2 inhibitors – can exert a renoprotective effect via a number of mechanisms; these include restoring the tubuloglomerular feedback mechanism and lowering glomerular hyperfiltration, and reducing inflammatory and fibrotic markers induced by hyperglycaemia, thus limiting renal damage. Simultaneous use of an SGLT-2 inhibitor and blockade of the renin–angiotensin–aldosterone system has thus emerged as a possible strategy to slow the progression of diabetic nephropathy, and several primary renal endpoint studies are ongoing to evaluate the efficacy and safety of this approach.

Injectable incretin therapy (glucose-like peptide (GLP)-1 receptor agonists) have also demonstrated promising results for improving predictors of renal disease, for example reducing albuminuria and any fall in eGFR. These drugs are not currently licensed for use in advanced kidney disease.

Education of patients on sick day rules (temporary suspension of drugs such as metformin, ACE inhibitors, diuretics, GLP-1 receptor agonists and SGLT-2 inhibitors, alongside increased fluid intake) is important and can prevent acute kidney injury.

No one particular class of glucose-lowering drug is currently recommended over another to help protect the kidney, and further research is needed to determine whether these newer agents protect the kidney to a greater degree.

There have been sporadic reports of acute kidney injury with injectable incretins and SGLT-2 inhibitors.

Insulin clearance through the kidney starts to fall when eGFR is <30 ml/minute (stage 4 kidney disease), and the risk of hypoglycaemia progressively increases. This may be compounded by reduced appetite and worsening nutritional status.

Blood pressure

Raised blood pressure has particularly damaging consequences for the kidney (and heart and retina). Current recommendations suggest that blood pressure should be lowered to 130/80 mmHg or less (although in younger patients, especially those with type 1 diabetes, sustained readings <125/80 mmHg are desirable to

further reduce proteinuria).[1] Non-pharmacological interventions such as dietary and lifestyle changes (e.g. restriction of salt and alcohol intake, weight reduction, increased exercise, stopping smoking) are important, although most patients require antihypertensive agents (often more than one) to achieve target blood pressures. Tighter blood pressure control in elderly individuals and those with evidence of heart disease can be associated with increased risk, and lowering systolic blood pressure to <130 mmHg in these individuals affords no extra benefit.

First-line treatment is usually with an inhibitor of the renin–angiotensin system. These agents are effective blood pressure-lowering agents in patients with diabetic nephropathy, and are more antiproteinuric than other classes of agent.[1–3] Overall, these agents reduce renal and cardiovascular risks, as well as disease progression. The evidence base is different in type 1 and type 2 diabetes, but the benefits appear similar in both.

First-line treatment in both type 1 and type 2 diabetes is usually an ACE inhibitor, although some authorities favour an ARB in individuals with type 2 diabetes in view of the greater evidence base. The combination of a diuretic or calcium channel blocker with an ACE inhibitor or ARB is often required to achieve blood pressure control. Recent evidence has shown that combinations of an ACE inhibitor and ARB should be avoided as this leads to a higher incidence of hyperkalaemia and acute kidney injury than the respective monotherapies, with no additional beneficial effect on progression of renal or cardiovascular disease.

After starting an ACE inhibitor or ARB, serum creatinine and potassium should be closely monitored (in the first 2–3 weeks), especially in patients with peripheral vascular disease. This is because of the possible coexistence of renal artery stenosis, which can produce a significant rise in serum creatinine of >30% from baseline. In patients with type 1 diabetes if particular, hyperkalaemia can be a particular concern in individuals with 'hyporeninaemic pseudohypoaldosteronism – type IV renal tubular acidosis', a defect at the aldosterone receptor in the kidney probably related to the development of autonomic neuropathy.

More than one antihypertensive agent is likely to be required. In type 2 diabetes with microalbuminuria, there is evidence that the combination of a low-dose thiazide with a renin–angiotensin system inhibitor can be beneficial.

Serum lipids

From the onset of microalbuminuria, cholesterol and triglycerides can be elevated in both type 1 and type 2 diabetes. Statin therapy should be considered for all patients with diabetic nephropathy.[2,3]

Changes in diet following healthy eating guidelines, weight reduction and improved metabolic control should be considered in all cases. In type 2 diabetes, statin therapy should be used to reduce total cholesterol to <4.0 mmol/litre and LDL-cholesterol to <2.0 mmol/litre in patients with diabetic nephropathy. It seems reasonable to extrapolate this to type 1 diabetes with microalbuminuria/overt nephropathy, given its association with premature cardiovascular disease.

Smoking is associated with the development and progression of diabetic nephropathy and with cardiovascular disease; it should be discouraged in all patients.

Protein restriction is controversial but has been shown to have a beneficial effect in type 1 diabetes with overt nephropathy and advanced kidney disease (stage 4 chronic kidney disease). Reductions in animal protein intake to 0.6–0.7 g/kg per day should be considered. Replacement of animal by vegetable protein sources can also be considered because vegetable protein seems to be less damaging to the kidney. An expert nutritionist should supervise all such treatment, and care should be taken to minimize any potentially detrimental effects. No prospective data are available for type 2 diabetes.

Associated complications

Microvascular and macrovascular complications can progress rapidly in patients with clinical albuminuria.

Retinopathy, neuropathy and atherosclerotic complications should be monitored more regularly, and any abnormalities treated promptly. Anaemia is common in diabetic nephropathy and can occur at an earlier stage of chronic kidney disease than in other kidney diseases, particularly in type 1 diabetes and in women.

Multifactorial treatment of diabetic nephropathy

It cannot be emphasized enough that the key is early detection. If any level of kidney disease is confirmed, an intensified multifactorial intervention addressing all the risk factors is essential. Care should be taken in frail patients, who might not tolerate aggressive intervention.

In patients with type 2 diabetes with microalbuminuria, sustained beneficial effects with respect to microvascular complications and cardiovascular disease and mortality have been reported using an approach with tight glucose and blood pressure regulation, and the use of renin–angiotensin system blockers, aspirin and lipid-lowering agents, using multiple drug combinations, along with behaviour modification. It is likely that type 1 diabetes would benefit similarly.[5]

Thus, early multifactorial intervention is key to reducing the burden of renal and cardiovascular complications in this population. It is important that clinicians monitor trends and changes in albuminuria and eGFR decline to identify those at high risk of progression of diabetic nephropathy; these patients often require more frequent monitoring, enhanced care and early referral to renal nephrology services.

Nephrological referral

Current guidelines suggest joint treatment by diabetes and renal specialists in the patients whose eGFR is <30 ml/minute, when the rate of progression is unduly fast (sustained decrease in GFR of 25% or more and a change in GFR category or sustained decrease in GFR of 15 ml/minute/1.73 m^2 or more within 12 months) and where atypical kidney disease is suspected.[4]

Late referral

Late referral (within 6 months of the need for renal replacement therapy) is associated with higher mortality.

Stage 5 kidney disease – end-stage renal failure

The mode of therapy (dialysis, transplantation) in end-stage renal failure depends on clinical judgement, and on local facilities and resources. Good glycaemic control is important for patients' well-being before and during renal replacement therapy, and is associated with lower mortality. There are limited data on appropriate target glucose levels in this population, and an

individualized approach to glycaemic control is required in view the high risk of hypoglycaemia in patients with advanced kidney disease.

In specialized centres, pre-emptive combined kidney and pancreas transplantation can be considered, usually for type 1 diabetes. Transplantation offers improved prognosis over dialysis. The outcome of renal replacement therapy remains poorer in patients with diabetic chronic renal failure than in those with non-diabetic disease.

In stage 5 kidney disease, interpretation of glycated haemoglobin concentration can be less reliable. Values should be interpreted with caution as reduced red cell lifespan can produce lower values, especially in patients undergoing haemodialysis.

Pregnancy and proteinuria

Development of microalbuminuria or macroalbuminuria during pregnancy in a woman with diabetes should alert the physician to the risk of pre-eclampsia. As ACE inhibitors and ARBs are potentially teratogenic, counselling and advice on contraception is essential in female patients of childbearing age who have nephropathy. Pregnancy is no longer contraindicated in women with diabetic proteinuria, but proteinuria can increase during pregnancy, and the risk of eclampsia is increased. Pre-pregnancy counselling and planning is vital. The risk of further loss of kidney function appears to be greatest in those whose eGFR is <50 ml/minute at conception or in whom proteinuria is present. Specialist renal pre-pregnancy counselling is advisable. ◆

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