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Learning objectives

After reading this article the participant should be able to:

1. Outline the basic pathophysiology of diabetic nephropathy.
2. Describe the natural history of diabetic nephropathy.
3. Discuss the diagnosis and staging of chronic kidney disease and nephropathy.
4. Know the evidence-based therapies for each stage of diabetic nephropathy.

Key words

- Diabetic nephropathy
- Glomerular filtration rate
- Macroalbuminuria
- Microalbuminuria

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UNIT 2 Comorbidities and complications

Diabetic nephropathy: Diagnosis, screening and management

Rudy Bilous

Diabetic nephropathy remains the most common single cause of end-stage renal failure and is associated with increased cardiovascular morbidity and mortality. This article discusses: the pathophysiology of nephropathy; its staging by albuminuria and estimated glomerular filtration rate; and the evidence for prevention and treatment. A multifactorial approach addressing known cardiovascular disease risk factors is required for most people with type 2 diabetes and nephropathy.

Diabetic nephropathy is one of the triad of specific microvascular complications in the eye, kidney and peripheral nerve, recognised as such in the 1950s (Root et al, 1954). The association between diabetic and renal abnormalities was known in the 19th Century but it was not until the description of nodular glomerulosclerosis by Kimmelstiel and Wilson in the 1930s that the pathological basis of nephropathy was established (Kimmelstiel and Wilson, 1936).

Diabetes is the most common single cause of end-stage renal failure worldwide and represents a major public health problem (Saran et al, 2015). Early identification and evidence-based intervention are critical to prevent development and to slow progression.

Pathophysiology

Although the kidneys are generally enlarged mainly owing to tubular hyperplasia, the histological appearance at diagnosis of type 1 diabetes is essentially normal. The earliest pathological abnormality is increased thickening of the glomerular capillary basement membrane due to an accumulation of matrix material (Osterby, 1992).

Nearly all people with diabetes will demonstrate

this abnormality after 10 years. A minority will show a steady increase in matrix in the areas between the capillaries (the glomerular mesangium), which eventually obliterates them and reduces the filtration capacity of the kidney, ultimately leading to organ failure (*Figure 1*) (Osterby, 1992). This process takes many years and the pathological features and clinical course are pathognomonic of diabetic nephropathy.

At some stage the capillaries will start to leak proteins (initially albumin, but larger molecules as nephropathy progresses) and these can be detected in the urine. Albuminuria is thus the earliest clinical feature of nephropathy (Marshall and Flyvbjerg, 2006).

As filtration surface is lost secondary to capillary occlusion by matrix material, then glomerular filtration rate gradually declines (at rates of 4–10 mL/min/year) and plasma creatinine and urea concentrations start to rise (Marshall and Flyvbjerg, 2006).

Finally, an important clinical correlate is systemic blood pressure, which rises as albuminuria increases and glomerular filtration declines. High blood pressure accelerates the pathological processes and is an important target for intervention (Marshall and Flyvbjerg, 2006).

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The same processes can be seen in type 2 diabetes and the pathological features in the kidney are broadly the same (White and Bilous, 2000). However, because the precise onset of hyperglycaemia is difficult to determine, individuals may have established nephropathy at diagnosis of diabetes. Moreover, many will have pre-existing vascular disease and hypertension, so there may be other causes of renal disease, such as ischaemia, and blood pressure may be high before diabetes develops.

Older people (particularly women) may have recurrent urinary tract infections, which may cause tubulointerstitial damage contributing to functional impairment. Thus, the natural history of kidney disease in people with type 2 diabetes can vary depending on the balance of underlying pathological causes (Fioretto et al, 1996).

Apart from hyperglycaemia and hypertension, there are other processes that are thought to contribute to nephropathy development (*Box 1*).

Diagnostic tests and staging

Albuminuria

Classically, the diagnosis of nephropathy depended upon the detection of proteinuria in a person with diabetes. The development of routine urine testing dipsticks for protein made diagnosis easier but these methods were only sensitive to an albumin concentration of around 300 mg/L.

The development of more sensitive assays for albumin in the 1980s demonstrated that people developing nephropathy had smaller increases in albuminuria long before the routine tests were positive. This phenomenon was termed “microalbuminuria” (not a great term as the albumin is the same but just present in smaller amounts) or “incipient nephropathy,” but is now called moderately elevated albuminuria (NICE, 2014). Traditional dipstick-positive albuminuria then became known as “macroalbuminuria” or overt (sometimes clinical) nephropathy, but is now called severely elevated albuminuria (NICE, 2014).

Consensus has defined the limits of normal, moderate and severe albuminuria based on timed urine collections (Royal College of Physicians of Edinburgh, 2007; Kidney Disease Outcomes Quality Initiative, 2012). However, these are cumbersome for individuals to collect and labour intensive to analyse,

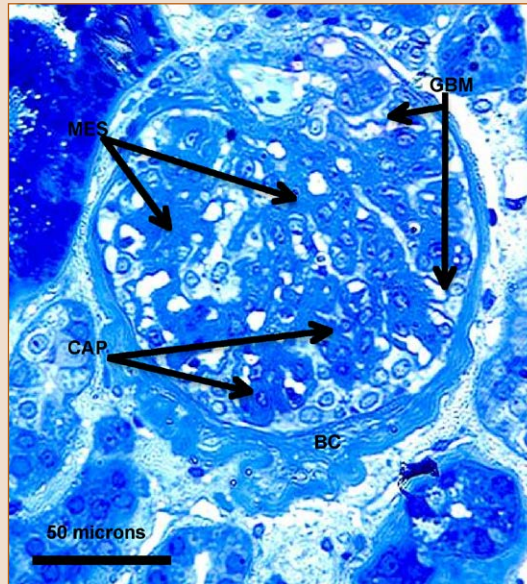


Figure 1. Photomicrograph of a glomerulus from a person with type 1 diabetes and macroalbuminuria. Note the thickened and split Bowman's capsule (BC), expansion of the mesangial (intercapillary) space (MES), thickened glomerular basement membrane (GBM) and capillary closure (CAP). Courtesy of Dr K White, Biomedical Electron Microscopy Unit, Newcastle University, Newcastle Upon Tyne.

so spot urine samples for albumin corrected for urinary concentration of creatinine (the albumin–creatinine ratio) have been adopted and diagnostic thresholds defined (*Table 1*).

It must be remembered that albuminuria is a continuous variable, so any cut-off point defining disease is slightly arbitrary and there will be false-positive and negative results, particularly at the upper or lower limits of disease or stage classification (see *Table 2*). The situation is further complicated because moderate albuminuria can be found: in people with hypertension but without diabetes; in the presence of urinary tract infections; in people with

Box 1. Potential causative factors for diabetic nephropathy.

Major factors	<ul style="list-style-type: none"> ● Hyperglycaemia ● Hypertension ● Renal haemodynamics ● Genes and ethnicity
Other factors	<ul style="list-style-type: none"> ● Mechanical stretch of the glomerular capillary basement membrane ● Structural factors ● Hyperlipidaemia ● Low birth weight ● Growth factors ● Smoking ● Endothelial dysfunction ● Dietary protein intake ● Obesity ● Hydrocarbon exposure

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Table 1. Classification of diabetic nephropathy by albuminuria (adapted from Kidney Disease Outcomes Quality Initiative, 2012).

Urine specimen	Moderate (micro) albuminuria	Severe (macro) albuminuria
Timed overnight collection	20–199 µg/min	≥200 µg/min
24-hour collection	30–299 mg/day	≥300 mg/day
Albumin concentration	20–300 mg/L	>300 mg/L
Albumin–creatinine ratio (ACR)	Men 2.5–30 mg/mmol Women 3.5–30 mg/mmol	>30 mg/mmol

NICE (2014) guidance on chronic kidney disease suggests that positive tests for microalbuminuria should be confirmed within 3–4 months before making a firm diagnosis of nephropathy. False-positive tests can occur after vigorous exercise, in the presence of infection or blood (e.g. menses), or with a concentrated urine (less of a problem with albumin–creatinine ratio). False-negative tests can occur with a diuresis. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy can reduce microalbuminuria into the normal range.

metabolic syndrome; and in ischaemic nephropathy or tubulointerstitial disease. It is therefore much less specific for nephropathy in type 2 diabetes although the presence of retinopathy in people with albuminuria makes underlying diabetic glomerulopathy much more likely (He et al, 2012). In addition, it is now realised

that increases, even within the normal range, may predict later development of nephropathy (Hovind et al, 2004), and there is considerable fluctuation such that those with moderate albuminuria may revert spontaneously to normal (Perkins et al, 2003). A list of the causes of false-positive and false-negative tests is shown in *Table 1* (see footnote).

Glomerular filtration rate

The detection of albuminuria is the cornerstone of diagnosis of nephropathy. However, of immediate relevance to the patient and clinician is glomerular filtration rate (GFR).

At diagnosis, GFR can be elevated in people with type 1 or 2 diabetes. This is often termed “hyperfiltration” and may contribute to later nephropathy development. The rate of decline of GFR thereafter determines the progression of nephropathy and likely timing of end-stage renal disease (ESRD) requiring renal replacement therapy. As it is important to plan this well in advance, then an estimate of GFR is clinically important. Precise estimates of GFR can be performed using infusions of neutral molecules,

Table 2. Stages of CKD and historical definition of DKD.

GFR stage, description and definition	Albuminuria stage, description and definition		
	A ₁ normal <3.0 mg/mmol	A ₂ moderate (micro) albuminuria 3.0–30 mg/mmol	A ₃ severe (macro) albuminuria >30 mg/mmol
G1 (normal) >90 mL/min/1.73 m ²	At risk for DKD*	Possible DKD (likely if DR)	Likely DKD especially if DR (consider other causes of albuminuria in type 2 diabetes)
G2 (mild decrease) 60–89 mL/min/1.73 m ²	At risk for DKD*	Possible DKD (likely if DR)	Likely DKD especially if DR (consider other causes of albuminuria in type 2 diabetes)
G3a (mild–moderate decrease) 45–59 mL/min/1.73 m ²	Possible DKD (probable if DR)	Likely DKD (definite if DR)	DKD
G3b (moderate–severe decrease) 30–44 mL/min/1.73 m ²	Possible DKD (probable if DR)	Likely DKD (definite if DR)	DKD
G4 (severe decrease) 15–29 mL/min/1.73 m ²	Possible DKD (probable if DR)	Probable DKD (likely if DR)	DKD
G5 (kidney failure) <15 mL/min/1.73 m ²	Likely DKD (definite if DR)	Probable DKD (likely if DR)	DKD

*Not CKD unless abnormal urinalysis and/or abnormal renal imaging present. CKD=chronic kidney disease; DKD=diabetic kidney disease; DR=diabetic retinopathy.

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such as inulin, and measuring their appearance in the urine (Stevens et al, 2006).

Infusion of filtration markers is clearly of limited routine utility. Endogenous creatinine, however, can serve almost as well. Creatinine is produced from muscle cells as part of normal metabolism and is completely filtered by the renal glomerulus. Under steady-state conditions, its production and excretion are in balance and it can be used as a filtration marker. A timed (usually 24-hour) urine collection can thus derive an estimate of GFR from creatinine clearance using the above formula. This estimate, however, is still dependent on a urine collection (Stevens et al, 2006).

As GFR declines, plasma creatinine concentrations will rise, but do not cross the upper limit of normal until there is significant loss of filtration capacity. In 1999, researchers used the patient database from the Modification of Diet in Renal Disease (MDRD) study to derive an equation that would convert a plasma creatinine concentration into an estimate of GFR (now called eGFR; Levey et al, 1999; 2009). An alternative method called the Cockcroft–Gault equation also exists but this estimates creatinine clearance, not GFR, and requires a measure of body weight. The four-point MDRD equation is:

eGFR=175 × (serum creatinine [µmol/L] × 0.0113)^{-1.154} × (age [years])^{-0.203}
(multiply by 0.742 if female; multiply by 1.21 if of African-Caribbean origin)

This estimated GFR has been used as a basis for diagnosis and staging of chronic kidney disease (CKD; Levey et al, 1999) and has been recently modified by the inclusion of grading of albuminuria (Kidney Disease Improving Global Outcomes, 2013). *Table 3* is adapted from the NICE (2014) guidelines on CKD and is a useful tool for determining the frequency of monitoring GFR for people with or at risk of CKD.

Creatinine has its limitations as a marker of filtration and this must be borne in mind when interpreting eGFR (*Box 2*). Moreover, eGFR tends to underestimate true GFR, particularly at values above 60 mL/min/1.73 m². However, eGFR is an important way of recognising impairment of renal function at low serum creatinine concentrations.

In addition, large intervention trials in people with cardiovascular (CV) disease have shown that a reduced eGFR is an independent risk factor for morbidity and mortality and this relationship is also true for people with diabetes (Anavekar et al, 2004; Go et al, 2004). In South Tees, mortality rates were twice as high in people with diabetes and an eGFR of <30 mL/min/1.73 m² compared with those with a value of >90 mL/min/1.73 m² (Nag et al, 2007). Thus, the detection of a falling eGFR should prompt rigorous management of CV disease risk factors.

Epidemiology

Incidence and prevalence of nephropathy depends on the diagnostic criteria and the population under study. Using albuminuria, reported transition rates from normal to moderate albuminuria are around 1–2% per annum and are about the same for type 1 and type 2 diabetes (Adler et al, 2003). However, these rates can be strongly influenced by other factors, such as duration of diabetes, ethnicity and presence of hypertension, CV disease or obesity. Transition rates from moderate to severe albuminuria are slightly higher at approximately 3% per annum, but this is heavily influenced by the baseline albuminuria – the higher this is, the greater the rate of transition (ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001).

Prevalence rates are much more variable and dependent on the population under study. In general, population-based studies (not confined to secondary care) report rates for moderate albuminuria of 12–27%, and 19–42% for type 1 and type 2 diabetes, respectively. For severe albuminuria the reported range is even wider at 0.3–24% for type 1 and 9–33% for type 2 diabetes (Bilous, 1996). These data refer to definitions of nephropathy based upon albuminuria; in the USA, the prevalence of CKD (combining albuminuria or a reduced GFR or both) in the general population with diabetes was around 2.3% for the period 2007–2012, up from 1.8% in 1994–1998 (Saran et al, 2015).

End-stage renal failure is easier to define but rates are not linear with duration. Using a national disease register, rates of 2.2% and 7.8% for people with type 1 diabetes with 20 and 30 years' duration, respectively, have been reported from Finland (Finne et al, 2005). For the UKPDS (UK Prospective Diabetes Study) cohort of people with newly

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Box 2. Limitations of plasma creatinine concentration as a marker of glomerular filtration.

- Can be increased following vigorous exercise, high-animal-protein meal, dehydration or acute kidney injury.
- Progressive kidney function decline leads to proportionally more tubular secretion, which over-estimates true glomerular filtration rate (GFR).
- Non-linear relationship with GFR so plasma concentration only increases once GFR significantly reduced (a doubling of plasma creatinine roughly equates to a halving of GFR).

diagnosed type 2 diabetes, 0.6% of people required renal replacement therapy or died from renal failure after 10.4 years of known diabetes duration (Adler et al, 2003; Bilous, 2008). Latest data from the UK Renal Registry for 2013 report an incidence rate of 25.4 per million population for diabetes as a cause of ESRD and a prevalence of 15.9% for those already on renal replacement therapy (UK Renal Registry, 2015).

The main reason for the discrepancy in rates of ESRD between type 1 and 2 diabetes is the increased CV mortality seen in people with nephropathy generally, and those with a reduced eGFR specifically.

In the UKPDS, mortality was two- to three-fold greater in those with moderate or severe albuminuria compared with normoalbuminuria. For those with a plasma creatinine >175 µmol/L or requiring renal replacement therapy, mortality was 14-fold greater (Adler et al, 2003). Thus, many people with nephropathy are dying before entering ESRD requiring renal replacement therapy.

Encouragingly, recent data from the US have suggested that incident rates of diabetic ESRD requiring renal replacement therapy have been declining since 1996 at around 3.4%/year/100 000 people with diabetes and this is particularly noticeable for type 1 diabetes. The reasons are unclear but probably reflect better overall diabetes and blood pressure management (Burrows et al, 2010) but may also be due to earlier detection and diagnosis of diabetes thus increasing the denominator and artificially reducing incidence rates. Unfortunately, prevalence rates of people with diabetes on renal replacement therapy continue to rise and now exceed 700 per million population with a steady year-on-year increase over the last decade (Saran et al, 2015).

Table 3. Recommended number of times per year GFR should be monitored according to the GFR and ACR stage of the individual, adapted from NICE (2014).

		ACR categories (mg/mmol) description and range		
		A ₁ <3 Normal to mildly increased	A ₂ 3–30 Moderately increased	A ₃ >30 Severely increased
GFR categories (ml/min/1.73 m ²), description and range	G1 ≥90 Normal and high	≤1	1	≥1
	G2 60–89 Mild reduction related to normal range for a young adult	≤1	1	≥1
	G3a 45–59 Mild–moderate reduction	1	1	2
	G3b 30–44 Moderate–severe reduction	≤2	2	≥2
	G4 15–29 Severe reduction	2	2	3
	G5 <15 Kidney failure	4	≥4	≥4

ACR=albumin-creatinine ratio; GFR=glomerular filtration rate.

Clinical features

There are no specific clinical features of nephropathy in its early stages. In people with type 1 diabetes a rise in blood pressure is a subtle sign but usually accompanies an increase in albuminuria (Marshall and Flyvbjerg, 2006).

The clinical features of established nephropathy are often dictated by concomitant comorbidities that can be diabetes specific (retinopathy and neuropathy) or due to macrovascular disease in the coronary, cerebral or peripheral vasculatures. The majority of people entering end-stage renal failure due to diabetic nephropathy will have evidence of some or all of these complications.

In only a minority of people does the proteinuria become so great as to lead to the nephrotic syndrome of hypoalbuminaemia, peripheral oedema, hypercholesterolaemia and heavy proteinuria. Such people have a poor prognosis from the cardiorenal perspective (Skupien et al, 2014).

As renal impairment gets worse, anaemia due to erythropoietin deficiency is more common and is said to occur earlier in people with diabetic

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nephropathy compared with those with non-diabetic kidney disease for any given GFR (Bosman et al, 2001). Prevalence studies suggest that around 15% of people with diabetes will have a World Health Organization-defined anaemia (<12 g/dL in premenopausal women; <13 g/dL for men), and these rates increase as GFR declines (Jones et al, 2010).

Hyperphosphataemia, hypocalcaemia and secondary hyperparathyroidism are also features of declining GFR and can lead to osteodystrophy and possibly contribute to macrovascular calcification.

As GFR declines towards CKD stage 5, symptoms of uraemia such as nausea, anorexia, pruritus, bad taste, tiredness and weight loss (sometimes masked by increasing peripheral oedema) develop. The occurrence of these is a sign that renal replacement therapy is imminent.

Management in primary care and when to refer

Tight glycaemic control is the only therapy shown to prevent development of moderate albuminuria in type 1 diabetes. The DCCT (Diabetes Control and Complications Trial) showed an approximately 50% reduction in moderate albuminuria after 9 years of tight control. This benefit continued for 8 years after the study completed despite the fact that HbA_{1c} levels were similar in the original intensively and conventionally treated cohorts during follow-up. Even after this duration of study, there was no significant impact on the numbers needing renal replacement therapy partly because there were so few events (DCCT/Epidemiology of Diabetes Interventions and Complications [EDIC] Research Group, 2003). Latest data from the same group have shown fewer individuals developing renal impairment (GFR <60 mL/min/1.73 m²) during follow-up, but rates of loss of GFR were similar in the intensive and conventionally treated groups (DCCT/EDIC Research Group, 2011).

For people with type 2 diabetes, the UKPDS showed a smaller but still significant reduction in incident moderate albuminuria in the intensively treated group. In addition, although the numbers were very small, fewer people had a doubling of their baseline serum creatinine (roughly equivalent to a halving of GFR) in the intensive arm (UKPDS Group, 1998a). The ACCORD (Ismail-Beigi et al, 2010) and ADVANCE (ADVANCE Collaborative

Group, 2008) studies showed some benefit of tight glycaemic control on development of albuminuria, but meta-analysis has failed to show benefit on hard end-points such as ESRD (Hemmingsen et al, 2011). Current guidance suggests a target HbA_{1c} level of <48 mmol/mol (<6.5%) in people with type 1 diabetes (NICE, 2015a). In type 2 diabetes, a target HbA_{1c} of 48 mmol/mol (6.5%) in those on a diet, with a threshold of escalation of therapy at 59 mmol/mol (7.5%), is suggested to prevent microvascular complications, but with consideration of the risk of hypoglycaemia, particularly in the elderly (NICE, 2015b). There is no conclusive evidence of an effect of tight glycaemic control on nephropathy development once moderate or severe albuminuria has developed, but the Joslin clinic (USA) has reported an association of slower rates of decline of GFR in those with better long-term glycaemic control (Skupien et al, 2014). NICE recommendations for kidney damage in type 2 diabetes are outlined in *Box 3*.

Once moderate or severe albuminuria has developed, blood pressure management is critical. All patients should be given general advice about reducing dietary salt and alcohol, weight reduction and increasing exercise. However, most will also require drug therapy.

Drugs that block the renin–angiotensin system (RAS) have not been consistently shown to prevent moderate albuminuria in people with type 1 or type 2 diabetes who have well-controlled blood

Box 3. Screening recommendations for kidney damage (NICE, 2014).

- Ask all people with or without detected nephropathy to bring in a first-pass morning urine specimen once a year. In the absence of proteinuria or urinary tract infection (UTI), send this for laboratory estimation of albumin–creatinine ratio (ACR). Request a specimen on a subsequent visit if UTI prevents analysis.
- Make the measurement on a spot sample if a first-pass sample is not provided (and repeat on a first-pass specimen if abnormal) or make a formal arrangement for a first-pass specimen to be provided.
- Measure serum creatinine and estimate the glomerular filtration rate (using the method-abbreviated Modification of Diet in Renal Disease four-variable equation) annually at the time of ACR estimation.
- Repeat the test if an abnormal ACR is obtained (in the absence of proteinuria or UTI) at each of the next two clinic visits but within a maximum of 3–4 months. Take the result to be confirming microalbuminuria if a further specimen (out of two more) is also abnormal (>2.5 mg/mmol for men; >3.5 mg/mmol for women).

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Page points

1. Cholesterol-lowering therapy and low-dose aspirin should be considered for individuals who have a 5-year cardiovascular disease risk >20% based upon the Framingham equation (Joint British Societies, 2014).
2. NICE has issued guidelines for the management of both type 1 and type 2 diabetes that include advice on diabetic nephropathy.

pressure and who are at low overall CV risk (Bilous et al, 2009). For hypertensive people, or those who have already had a CV event, then angiotensin-converting enzyme (ACE) inhibitors have been shown to prevent the development of severe albuminuria (Heart Outcomes Prevention Evaluation Study Investigators, 2000).

Once people have persistent moderate albuminuria then ACE inhibitors in type 1 diabetes and angiotensin receptor blockers (ARBs) in type 2 diabetes reduce progression to severe albuminuria and increase regression to normoalbuminuria over and above their blood pressure-lowering effect (ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001; Parving et al, 2001). However, none of these studies were powered to detect any impact on rates of ESRD development. There is, however, good evidence of benefit of ACE inhibitor therapy once people with type 1 diabetes have severe albuminuria and a reduced GFR (Lewis et al, 1993). In those with type 2 diabetes the effect is smaller but still significant and has only been conclusively established for ARBs (Brenner et al, 2001; Lewis et al, 2001). Meta-analysis has confirmed these benefits (Palmer et al, 2015).

The UKPDS showed that many people with type 2 diabetes require three or more drugs to control their blood pressure to target, so although RAS blockade forms the cornerstone of therapy, other agents will almost certainly need to be added (UKPDS Group, 1998b).

A high dietary salt intake will reduce the effectiveness of RAS blockers so reduction should be reiterated for all people taking them. Diuretics

work synergistically with RAS-blocking agents. For people with CKD stage 3 or worse then loop diuretics rather than thiazides are indicated. Calcium-channel blockers are the next agent recommended in the British Hypertension Society guidelines, but beta-blockers are also useful in people with a history of ischaemic heart disease or heart failure (NICE, 2013; Joint British Societies, 2014). Concerns about their use in people with hypoglycaemia unawareness are probably overstated, although it is prudent to use cardioselective agents.

Current hypertension guidance suggests a blood pressure target of <130/80 mmHg (Joint British Societies, 2014), although these targets have been called into question recently (Mahmoodi et al, 2012) and there may be little gain and even possible harm in reductions <140/90 mmHg. Control can be difficult to achieve without polypharmacy to a degree that has intolerable side effects or poses a problem for concordance and compliance. However, any reduction in blood pressure is of potential benefit, so it is critical to negotiate acceptable targets with people on an individual basis. A Cochrane review has found a reduction in dietary protein to be beneficial in terms of slowing nephropathy progression (Robertson et al, 2007).

As most people with diabetes and nephropathy have macrovascular disease, a small minority will have a functional renal artery stenosis. Renal blood flow in these people is dependent upon a functioning RAS so inhibition using ACE inhibitors or ARBs can result in an acute deterioration of renal function. For this reason, it is recommended that serum creatinine and potassium are checked within 2 weeks of initiation of RAS blockade and after any increase in dose (NICE, 2013; 2014; Joint British Societies, 2014). A rise in serum creatinine of >75 µmol/L should raise the possibility of renal artery stenosis. Increases less than this are common and not usually of clinical significance.

Because people with nephropathy have an increased risk of CV disease, cholesterol-lowering therapy and low-dose aspirin should be considered for all using the newer lifetime CV risk calculator which takes into account the presence of CKD (Joint British Societies, 2014). In reality, most people with diabetic nephropathy will have evidence of pre-existing macrovascular complications and should be prescribed such therapy for secondary

Box 4. When to refer to secondary care (adapted from Joint Specialty Committee on Renal Medicine, 2006).

- Chronic kidney disease stage 4 or 5 (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²).
- Rapid loss of GFR (>5 mL/min/1.73 m²/year or >10 mL/min/1.73 m²/5 years).
- Microscopic haematuria.
- Heavy proteinuria (>1 g/day or protein-creatinine ratio >100 mg/mmol) – especially if sudden onset or associated with nephrotic syndrome or in the absence of retinopathy.
- Features of other systemic disease (e.g. rheumatoid arthritis, systemic lupus or cancer).
- Further guidance is available from the Royal College of General Practitioners website (www.rcgp.org.uk; accessed 20.03.13).

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prevention anyway.

People with nephropathy are at high risk of foot ulceration and many will have established retinopathy. It is important that they continue to access foot and retinal screening.

The Steno-2 Study (Gaede et al, 2008) of multifactorial CV risk intervention in people with type 2 diabetes with moderate albuminuria at baseline demonstrated long-term benefits on mortality, development of nephropathy and ESRD, as well as CV complications, including myocardial infarction and amputation. The treatment included RAS-blocking drugs in all participants in the intensively treated group, lipid-lowering therapy with a target total cholesterol <4.5 mmol/L, intensive glycaemic control with a target HbA_{1c} level of <48 mmol/mol (<6.5%), low-dose aspirin, antioxidants (vitamins C and E) and lifestyle changes, including stopping smoking, weight reduction and increasing exercise. As with the DCCT/EDIC and UKPDS, these benefits continued beyond the end of the trial.

NICE has issued guidelines for the management of both type 1 and type 2 diabetes that include advice on diabetic nephropathy (NICE, 2015a; 2015b). Moreover, there is guidance for CKD generally, which also includes a section on diabetes (Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, Royal College of General Practitioners, 2006; NICE, 2014).

When to refer?

The Royal College of General Practitioners has issued guidance on the indications for referral for people with CKD (Joint Specialty Committee on Renal Medicine, 2006; *Box 4*). People with chronic, stable renal impairment and well-controlled glycaemia and blood pressure probably do not need referral even if they are at CKD stage 4. However, any person in whom glycaemia or blood pressure control is proving difficult and/or who has a rapidly declining GFR of >5 mL/min/year or >10 mL/min/5 years should be referred as they are at risk of requiring renal replacement therapy and this needs to be planned early. Similarly those with anaemia or calcium and phosphate problems should also be referred.

People with type 2 diabetes can also develop

Box 5. Case example one.

Narrative

Fred is 59 and has had type 2 diabetes for 6 years. Lately he has struggled with his blood glucose control and his HbA_{1c} level has gradually crept up to 81 mmol/mol (9.6%). His current treatment is metformin 500 mg three times daily and gliclazide 120 mg twice daily. He weighs 92 kg and has a BMI of 29 kg/m². He works as a taxi driver and does not drink alcohol or smoke. His blood pressure is 152/94 mmHg on repeat measurements. His estimated glomerular filtration rate is 65 mL/min/1.73 m² and his albumin–creatinine ratio was 5.7 and 7.8 mg/mmol on the last two tests. Retinal photography shows minimal background retinopathy. His plasma cholesterol is 6.2 mmol/L with an estimated low-density lipoprotein cholesterol of 3.6 mmol/L. His only other medication is ramipril 5 mg a day. How would you reduce his renal risk?

Discussion

Fred has retinopathy so his abnormal albumin–creatinine ratio almost certainly means that he has established nephropathy. At this stage effective blood pressure control and full renin–angiotensin system blockade is critical. He is on a submaximal dose of ramipril so this should be doubled to 10 mg a day and his plasma creatinine checked within 2 weeks. At the same time he should see the dietitian and nurse to see if he can lose weight and to check the salt content of his diet. Remember that most dietary salt is hidden in foods such as breads, pizzas and cereals. Fred's cardiovascular risk is >20% over the next 10 years, so he would benefit from a statin but there is no evidence of benefit as yet for low-dose aspirin. Improved glycaemic control would help prevent retinopathy progression. Insulin use may not be compatible with his job, so the addition of pioglitazone (although this can cause weight gain), a glucagon-like peptide-1 receptor agonist or a dipeptidyl peptidase-4 inhibitor could be considered (there are differences within each of these classes regarding renal restrictions relating to the prescribing of the agents, and so readers are advised to familiarise themselves with relevant prescribing information). Although he is not quite on maximal metformin and gliclazide, a further increase would be unlikely to achieve his glycaemic target. Fred needs to know about his cardiorenal risk and the importance of adherence should be emphasised. He may well need support or even counselling to come to terms with his condition.

Box 6. Case example two.

Narrative

Kylie has type 1 diabetes of 15 years' duration and is 21 years old. At her regular review she reports frequent hypoglycaemia, particularly during working hours as a waitress. Her HbA_{1c} level is 77 mmol/mol (9.2%) and she admits that she finds it hard to take her insulin regularly at work. Her blood pressure is 118/74 mmHg and her albumin–creatinine ratio is 2.8 mg/mmol. Kylie is on the oral contraceptive pill and should be taking short-acting insulin three times daily and a night-time long-acting insulin analogue. Her latest retinal photograph shows early background retinopathy. What are the priorities of treatment to prevent nephropathy?

Discussion

Improvement of Kylie's glycaemic control is critical. The Diabetes Control and Complications Trial (DCCT) showed that intensive glycaemic control (average achieved HbA_{1c} level of 53 mmol/mol [7.0%]) reduced the risk of developing microalbuminuria by >40% (DCCT/ Epidemiology of Diabetes Interventions and Complications [EDIC] Research Group, 2003). For retinopathy, the benefit was greater the higher the baseline HbA_{1c}, but it is not known if this is true for nephropathy. The concern is hypoglycaemia, which is likely to increase as HbA_{1c} improves. Options for Kylie include education programmes such as DAFNE (Dose Adjustment For Normal Eating), dietetic referral to learn or refresh carbohydrate counting, or an insulin pump. (It should be noted that retinopathy can temporarily worsen with improved glycaemia so repeat photography in 6 months is recommended.) Latest evidence from renal biopsy studies suggest that retinopathy is a sensitive marker of pathological damage in the kidneys (Klein et al, 2005). Therefore, although her albumin–creatinine ratio is normal, Kylie is at increased risk of nephropathy and needs to know this.

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“Nephropathy is a serious complication of diabetes and is associated with significant mortality and comorbidity. However, there is a strong evidence base for therapies that can prevent development and slow its progression.”

renal disease other than nephropathy and should be referred if they show any of the unusual features outlined in *Box 4*. The presence of retinopathy in a person with diabetes and albuminuria makes a diagnosis of diabetic nephropathy almost certain (He et al, 2012).

Psychological aspects

For many people with diabetes, the diagnosis of nephropathy and possible renal failure is an ominous one. Most will be aware of the implications and will show a classic bereavement reaction similar to that seen following a diagnosis of cancer or heart disease. For these reasons it is important to prepare people and their partners, carers and families well in advance of the need for renal replacement therapy. Many renal units offer pre-end-stage education and counselling as part of preparation for dialysis. For younger people, live donor kidney transplantation may be an option and requires careful and sensitive management.

Box 5 and *Box 6* provide case examples that highlight some of the practical issues related to the management of people with diabetic nephropathy.

Conclusion

Nephropathy is a serious complication of diabetes and is associated with significant mortality and comorbidity. However, there is a strong evidence base for therapies that can prevent development and slow its progression. Thirty years ago the median time from development of severe albuminuria to ESRD was just 7 years (Watkins et al, 1977) – it is now closer to 20 years. Moreover, the numbers of people requiring renal replacement therapy appear to be falling, at least in the US. This is probably the result of better overall care in terms of glycaemia and blood pressure and CV risk factor management. The remaining challenge is to try to prevent people developing nephropathy in the first place. ■

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. Ten years after the diagnosis of type 1 diabetes, what APPROXIMATE percentage of people are likely to have pathological thickening of the glomerular basement membrane? Select ONE option only.

- A. <10
- B. 33
- C. 50
- D. 66
- E. >90

2. In which ONE of the following situations is the finding of microalbuminuria MOST LIKELY to represent a false-positive result? Select ONE option only.

- A. A 21-year-old man with type 1 diabetes who was admitted with diabetic ketoacidosis 10 days before the test was taken
- B. A 37-year-old woman with type 1 diabetes who was on day 14 of her menstrual cycle when the test was taken
- C. A 42-year-old man with type 2 diabetes who undertook gentle walking exercise for 30 minutes immediately before the test
- D. A 55-year-old man with type 2 diabetes and hypertension who takes regular candesartan 16 mg each morning
- E. A 78-year-old female with type 2 diabetes who is taking trimethoprim for an intercurrent urinary tract infection

3. Which is the MOST LIKELY source of serum creatinine? Select ONE option only.

- A. Gastrointestinal tract
- B. Kidney
- C. Liver
- D. Muscle
- E. Skin

4. The eGFR calculation is derived from the MDRD study. Which ONE of the following is NOT included in

the modification of the original study algorithm? Select ONE option only.

- A. Age
- B. BMI
- C. Ethnicity
- D. Gender
- E. Serum creatinine

5. At which level (mL/min/1.73 m²) is the eGFR MOST LIKELY to UNDERESTIMATE true glomerular filtration rate? Select ONE option only.

- A. 21–30
- B. 31–40
- C. 41–50
- D. 51–60
- E. 61–70

6. According to the UKPDS study, what APPROXIMATE percentage of people are likely to have required a renal transplant or died from renal failure 10 years after their diagnosis of type 2 diabetes? Select ONE option only.

- A. 0.5
- B. 2.5
- C. 5
- D. 7.5
- E. 10

7. A 73-year-old woman with type 2 diabetes has significant diabetic nephropathy. She has normocytic anaemia. Which is the MOST LIKELY deficiency causing her anaemia? Select ONE option only.

- A. Aldosterone
- B. Erythropoietin
- C. Folate
- D. Renin
- E. Vitamin B₁₂

8. A 62-year-old male smoker with type 2 diabetes and diabetic

nephropathy develops nephrotic syndrome. Which of the following clinical findings is LEAST expected in this situation? Select ONE option only.

- A. Hypoalbuminaemia
- B. Hypocholesterolaemia
- C. Peripheral arterial disease
- D. Peripheral oedema
- E. Proteinuria

9. A 57-year-old woman with type 2 diabetes has a declining eGFR over several years and has recently noticed that the tips of her fingers are painful. Which of the following are the MOST LIKELY expected blood results? Select ONE option only.

	Phosphate	Calcium	Parathyroid hormone
A.	Low	Low	Low
B.	Low	High	Low
C.	Normal	Normal	Normal
D.	High	Low	High
E.	High	High	High

10. A 51-year-old man with type 2 diabetes and hypertension has recently started ramipril 2.5 mg once daily. Which of the following is the MOST LIKELY indication that he has underlying renal artery stenosis? Select ONE option only.

- A. Decrease in blood pressure since starting ramipril
- B. No change in blood pressure since starting ramipril
- C. Increase in blood pressure since starting ramipril
- D. Increase in serum creatinine (>75 µmol/L) since starting ramipril
- E. Increase in eGFR (>25 mL/min/1.73 m²) since starting ramipril