Renal complications of diabetes

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Introduction: Diabetic nephropathy is a leading cause of chronic kidney disease (CKD) in the UK. These patients are at significantly increased risk of cardiovascular disease and of progression to end-stage renal disease. We review the epidemiology, pathogenesis and natural history of diabetic nephropathy and evaluate the therapeutic options available.

Sources of data: We searched Medline and PubMed for source articles relevant to diabetic nephropathy and CKD.

Areas of agreement: Early multifactorial intervention including strict blood pressure control, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin two-receptor blockers (A2RB’s) and good metabolic control attenuates cardiovascular risk and slows the rate of progression of renal disease.

Areas of controversy: Current areas of uncertainty include the relative benefits of ACE inhibitors and A2RBs in combination, whether direct renin inhibitors are harmful in patients with diabetes and also the positioning of hypoglycaemic agents as renal function declines.

Growing points: What are the appropriate metabolic and blood pressure targets for patients with diabetes?

Areas timely for development: Therapeutic strategies as kidney function declines.

Keywords: diabetes/CKD/nephropathy

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Introduction

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD) in the UK, and the second most common cause of end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) or kidney transplantation.¹ This patient group are at significant cardiovascular risk and usually succumb to this, rather than progress to ESRD, especially patients with type 2 diabetes (T2DM).
Classically, DN is defined as an increase in urinary albumin excretion, accompanied by rising blood pressure and a decline in glomerular filtration rate (GFR). The classical pathological staging of DN in patients with Type 1 diabetes (T1DM) was described by Mogensen et al., who divided DN into five stages. The first stage being hyperfunction and hypertrophy with increased urinary albumin excretion. Stage 2 being associated with histological morphologic lesions, increased GFR and urinary albumin excretion (UAE) with exercise. Stage 3 being incipient diabetic nephropathy with abnormal UAE rates, detectable by radioimmunoassay. Stage 4, being overt DN and UAE >0.5 g/24 h. Stage 5 being ESRD with uraemia.

More recently, the National Kidney Foundation (NKF) recommend clinical staging of CKD according to eGFR values (see Table 1). This classification has been adopted by the Renal Association, and the National Institute for Health and Clinical Excellence (NICE) in the UK guidelines for the identification, management and referral of adults with CKD.

In this article we will discuss the epidemiology, pathophysiology, clinical presentation and management of diabetic nephropathy.

### Epidemiology

The incidence of ESRD in the UK has doubled in the past 10 years and is projected to continue rise. The increasing incidence of T2DM is contributing significantly to this. The number of patients with ESRD actually underestimates the entire burden of CKD. In a cross-sectional study of ~34 000 adults with diabetes in London, prevalence of CKD stages 3–5 was 18%. In another study of 7596 people with diabetes from Salford stage 3–5 CKD was observed in 27.5%.

### Natural history of diabetic nephropathy

Fundamental differences in the clinical phenotype between patients with T1DM and T2DM are recognised. Similarly, the clinical

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Table 1 Stages of CKD.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increase in GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with normal or mild reduction in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3a</td>
<td>Moderate reduction of GFR</td>
<td>45–59</td>
</tr>
<tr>
<td>3b</td>
<td>Severe reduction in GFR</td>
<td>30–44</td>
</tr>
<tr>
<td>4</td>
<td>Established renal failure</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Established renal failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

*aUse the suffix (p) to denote the presence of proteinuria when staging CKD.*

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manifestations of DN are different between these two patient groups. In T1DM, DN may typically present with the classical manifestations described by Mogensen *et al.*  Although patients with T2DM can present with a classical pattern, usually they have significant co-morbidity which often pre-dates the T2DM. Patients may be obese, hypertensive or have cardiovascular disease. They may have features of hypertensive nephropathy or renovascular disease. As such nephropathy in this group is often a mixed picture attributable to multiple aetiologies. This heterogeneity, impacts on the clinical manifestations. The pathological changes of nephropathy described in type 2 diabetes include glomerulosclerosis, non-specific chronic damage related to vascular changes and glomerular diseases superimposed on, or even unrelated to, diabetic glomerulosclerosis.  

The earliest biochemical manifestation of DN is the appearance of albuminuria, this being the most sensitive marker of CKD due to diabetes, glomerular disease or hypertension. Microalbuminuria refers to the excretion of albumin above the normal rate, but below the conventional levels of measurement by dipstick testing. Longitudinal studies suggest progression from normoalbuminuria to microalbuminuria occurs at a rate of 4% per year. Though baseline UAE, systemic blood pressure and serum cholesterol may all influence such progression, it is glycaemic control which appears key in reducing the incidence of microalbuminuria.  

In those with persistent microalbuminuria the rate of progression to macroalbuminuria varies from 5 to 10% per year, with ~20% of patients having macroalbuminuria at 5 years. It might be supposed that those factors which influence the rate of progression to macroalbuminuria would be similar to those for microalbuminuria; results have however proven inconsistent. Improved glycaemic control may retard progression, though control of blood pressure may be of greater significance. Established albuminuria then promotes further deterioration in renal function, studies have shown that albumin normally filtered by the glomerulus cause injury to tubular cells, leading to tubulointerstitial fibrosis, with the rate of decline in renal function directly related to the level of albuminuria.

**Pathogenesis of diabetic nephropathy**

In patients with diabetes, the cells of all tissues are exposed to hyperglycaemia. Whilst not all are equally susceptible, mesangial cells are exquisitely sensitive to the toxic effects of hyperglycaemia. However, not all patients with diabetes develop DN thus other factors must be of significance in the development of DN, and are thought to include
Familial/genetic

Familial clustering of DN is recognized, with a higher incidence in siblings of subjects with T1DM and nephropathy compared with siblings of probands without nephropathy. Several genes have been proposed as candidates for susceptibility to diabetic nephropathy. The gene encoding angiotensin-converting enzyme (ACE) has a polymorphism. A small group of patients with the type II genotype were found to have a 51.3% reduction in AER after 2 years of therapy with lisinopril compared with a 7.7% reduction in the DD genotype group.

Haemodynamic factors

Renal hyperperfusion and hyperfiltration can occur in newly diagnosed diabetes. However, several observations in patients with T1DM support the notion that renal hyperperfusion and hyperfiltration contribute to renal damage. Evidence that glomerular haemodynamic abnormalities contribute to the development of DN is provided by studies which have manipulated intra-glomerular pressure independent of metabolic control.

Biochemical

Hyperglycaemia is central to the pathogenesis of DN. Intracellular hyperglycaemia leads to the production of reactive oxygen species, a common mediator of the pathophysiology of hyperglycaemia and subsequent nephropathy. Increased oxidative stress activates glycation and formation of advanced glycation end products (AGEs), cytokines and growth factors via mechanisms including:
- increased polyol pathway flux,
- intracellular production of AGEs,
- protein kinase C (PKC) activation.

Increased polyol pathway flux

Hyperglycaemia increases glucose flux through the polyol pathway. This process consumes the cofactor NADPH, which is essential for regenerating the intracellular antioxidant reduced glutathione. By
reducing the amount of glutathione the polyol pathway increases susceptibility to oxidative stress.\textsuperscript{21}

**Intracellular production of AGEs**

AGE precursors damage cells by three mechanisms. Intracellular proteins involved in gene transcription are modified.\textsuperscript{23,24} Signalling between cells is influenced leading to cellular dysfunction.\textsuperscript{25} Circulating proteins are modified and bind to AGE receptors leading to production of inflammatory cytokines and growth factors which produce vascular damage.\textsuperscript{26}

One such cytokine is transforming growth factor-\(\beta\)\textsubscript{1} (TGF-\(\beta\)\textsubscript{1}) which is most highly expressed in the kidney. TGF-\(\beta\) has a central role in the sclerotic process of glomerulopathy.\textsuperscript{27} Treatment of patients with T2DM and DN with the ACE inhibitor perindopril led to a reduction in renal TGF-\(\beta\) gene expression and its downstream activation.\textsuperscript{28}

**PKC activation**

Intracellular hyperglycaemia increases PKC activity, which effects gene expression. PKC is a crucial downstream mediator of TGF-\(\beta\)\textsubscript{1}. Studies have demonstrated that prevention of albuminuria by ACE inhibitor treatment in diabetic rats was associated with normalization of glomerular PKC activity.\textsuperscript{26}

**Management of diabetic nephropathy**

The NICE clinical guideline 73 for the management of CKD\textsuperscript{4} is endorsed by the Renal Association for the detection and management of DN. It is recommended that all patients with diabetes undergo regular surveillance by spot urine testing for albuminuria, and measurement of serum creatinine for the estimation of GFR.

Recommendations for patients with microalbuminuria or proteinuria are as follows:

1. Achievement of HbA\textsubscript{1c} targets of 6.5–7.5%.
2. Prescription of ACE inhibitors titrated to full dose.
3. Control of hypertension to below 130/80 mmHg.
4. Timely referral to a nephrologist.

**Detection**

GFR is the best measure of the filtering capacity of the kidneys, with any change in a good index of progression of CKD. The Modification of Diet in Renal Disease (MDRD) equation which utilizes age, gender
and ethnicity to estimate GFR\textsuperscript{29} has gained favour in the majority of international guidelines for estimation of GFR. However, it does tend to underestimate higher levels of GFR.\textsuperscript{30}

Albuminuria is a more sensitive marker than total protein for DN. It is defined by a rise in urinary albumin loss to between 30 and 300 mg a day. Timed urine collections may be inaccurate and therefore the measurement of spot urine testing (ideally first voided sample) has largely replaced the longstanding timed urine collections. A urinary albumin/creatinine ratio (ACR) of >2.5 mg/mmol in men and >3.5 mg/mmol in women is used to define microalbuminuria, with the ACR values of >25.0 mg/mmol reflecting macroalbuminuria.

Quantitative measurement of ACR also allows for longitudinal monitoring of the degree of albuminuria. Increasing levels suggest worsening kidney function, whilst decreasing levels of albuminuria suggest lower risk of decline in kidney function.

**Treatment**

To attenuate the progression of DN, multifactorial therapeutic interventions are recommended. Here we will outline the evidence behind these management strategies.

**Glycaemic control**

The Diabetes Control and Complications Trial\textsuperscript{10} of patients with T1DM and normal UAE demonstrated that after 9 years of follow-up, intensive therapy (mean HbA\textsubscript{1c} of 7.2\%) had a 39\% adjusted risk reduction in new onset microalbuminuria and 54\% adjusted risk reduction in new onset macroalbuminuria. After 16 years, the intensive treatment group had a significantly lower rate of impaired renal function, defined as an eGFR of <60 ml/min per 1.73 m\textsuperscript{2} than the conventionally treated group.\textsuperscript{31}

The UK Prospective Diabetes Study (UKPDS) examined if intensive blood glucose control reduces the risk of micro and macrovascular complications in patients with newly diagnosed T2DM.\textsuperscript{9} The intensive-ly treated arm obtained a mean HbA\textsubscript{1c} of 7 versus 7.9\% in the conventional arm. A 25\% risk reduction in microvascular endpoints was seen with intensive treatment. This included a risk reduction of 34\% for progression of albuminuria and 67\% in the proportion of patients having a doubling of serum creatinine concentration.\textsuperscript{9}

The 10-year post-trial observational follow-up study of UKPDS participants was published in 2008,\textsuperscript{32} the benefits of early intensive
glycaemic control were shown to persist after the period of strictest intervention.\textsuperscript{32}

More recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was studied in over 10,000 patients with long-standing T2DM who were divided into intensive glycaemic control (median HbA$_{1c}$ of 6.4%) and standard glycaemic control group (median HbA$_{1c}$ of 7.5%). Unexpectedly and due to higher mortality rates in the intensive therapy arm, the study was terminated after a median follow-up of 3.6 years. At this point all subjects were converted to standard therapy. However, after 5 years, there remained a significant decrease in the incidence of microvascular renal outcomes in those who were initially intensively treated.\textsuperscript{33}

• Oral hypoglycaemic agents.

Multiple therapeutic options exist for management of hyperglycaemia in patients with diabetes. Kidney function should be evaluated prior to initiating any anti-diabetic therapy, as kidney disease will dictate the choice and dosage of medication. Patients with stage 3–5 CKD are particularly susceptible to hypoglycaemia especially when taking renally excreted medication. Patients with CKD should monitor blood glucose levels more frequently and may need a reduction in the dose of medication.\textsuperscript{34}

According to the British National Formulary, Metformin can be used in patients with mild-to-moderate renal impairment,\textsuperscript{34} although there is a theoretical risk of lactic acidosis. NICE recommends that the dose should be reviewed if eGFR is $<$45 ml/min/1.73 m$^2$ and that it should be avoided in those with eGFR $<$30 ml/min/1.73 m$^2$.

Sulphonylureas should be used with caution in patients with mild-to-moderate renal impairment, because of the hazard of hypoglycaemia. Long-acting sulphonylureas should be avoided in severe renal impairment.

Pioglitazone is now the only thiazolidinedione licensed for use in patients with diabetes. It can be used in renal impairment with no dose adjustment required. However, caution needs to be exercised, as this medication is associated with fluid retention and heart failure which is potentially hazardous in advanced CKD.

Studies have also shown an associated increased fracture risk in women. This has implications in people with advanced stages of CKD who may have renal bone disease. Pioglitazone should not be used in women with low bone mineral density or other risk factors for fracture.\textsuperscript{35,36}

Another concern is the potential increased risk of bladder cancer with pioglitazone. MHRA advocates that pioglitazone should not be
used in patients with active bladder cancer, a history of bladder cancer or uninvestigated haematuria.\textsuperscript{60}

Currently, there are four dipeptidyl peptidase 4 inhibitors approved for clinical use in the UK: sitagliptin, saxagliptin, vildagliptin and linagliptin. All four drugs have approval for use in patients with renal failure. Dose adjustment is required for sitagliptin, vildagliptin and saxagliptin. Only linagliptin does not require dose adjustment in renal impairment as it is primarily excreted via bowel and liver.\textsuperscript{34}

The glucagon-like peptide 1 (GLP-1) agonists, Exenatide (Byetta) and Exenatide Extended release (Bydureon) can be used in patients with mild renal impairment. The once daily GLP 1 agonist liraglutide (Victoza) can also be used in patients with mild renal impairment. However, the use in patients with an eGFR <60 ml/min/1.73 m\textsuperscript{2} is not recommended.\textsuperscript{34}

Often patients with advanced stages of CKD require insulin therapy. It should be remembered that insulin clearance is impaired with an increased half-life as renal failure progresses, hence insulin doses should be titrated to achieve adequate glycaemic control whilst striving to avoid hypoglycaemia.

**Hypertension**

Systolic and diastolic hypertension markedly accelerate the progression of nephropathy, and aggressive blood pressure control has been shown to reduce the rate of decline in GFR.\textsuperscript{37}

**Primary prevention**

Reducing blood pressure has been shown to reduce the risk of microalbuminuria and nephropathy in T2DM. Both ACE inhibitors and A2RB are effective in delaying the progression of renal disease, even in normotensive patients.\textsuperscript{9,37,38} In the Diabetic Retinopathy Candesartan Trials, of 725 normotensive patients with T2DM, candersartan reduced the rate of progression to microalbuminuria by 4.7 years.\textsuperscript{39} However, studies failed to demonstrate the renal benefit of ACE inhibitor or A2RB in patients with T1DM who were normotensive and normoalbuminuric.\textsuperscript{40,41}

**Secondary prevention**

Once nephropathy is established as evidence by albuminuria, effective control of hypertension is generally regarded as the best inhibitor of
Inhibitors of the renin–angiotensin system are recommended as first-line therapy; however, most patients require multiple agents to achieve satisfactory blood pressure control.

In the Irbesartan Diabetic Nephropathy Trial, 1715 patients were randomly assigned to irbesartan, amlodipine or placebo. After follow-up of 2.6 years, patients on irbesartan had lower risk of combined renal endpoints: defined as doubling of the plasma creatinine, development of end-stage renal disease or death from any cause. Reduction of systolic blood pressure < 120 mmHg was associated with increased cardiovascular mortality and with no renal benefit.37

Studies concluded that lowering blood pressure to a certain extent not only improves renal outcome but also has positive effect on cardiovascular morbidity and mortality.34,37

Current guidelines suggest systolic blood pressure of 130 mmHg and diastolic blood pressure of 80 mmHg in diabetic patients with renal disease.4,43 Some evidence supports a target blood pressure of < 125/75 mmHg;14 however, caution must be exercised as there is concern that in those who achieve a blood pressure < 120 mmHg there may be an overall increase in all cause mortality.37

Similar to glycaemic control, target blood pressure should also be individualized. Choice of first-line anti-hypertensive should be an ACE inhibitor in patients with T1DM and ACE inhibitor or A2RB in patients with T2DM.4,43

**Proteinuria**

Proteinuria is considered an independent risk factor for progressive renal disease. Agents, which attenuate proteinuria, are central to the management of diabetic nephropathy. ACEI produce the greatest reduction in urinary protein excretion, independent of reduction in the mean arterial blood pressure.44 The effect of agents such as diuretics, beta-blockers and calcium channel antagonists has effects, which is intermediate between that of ACEI and of placebo on proteinuria.44 The ARBs have a similar effect to ACEI in reducing UAE.

Valsartan has been shown to reduce UAE and promote regression to normoalbuminuria in patients with T2DM and microalbuminuria.45 In the RENAAL study conducted in patients with T2DM showed that in those treated with Losartan, there was a 25% reduction in the doubling of serum creatinine concentration, a 35% reduction in the level of proteinuria and a 28% reduction in risk of ESRD.46
Combination therapy with ACE inhibitors and A2RB’s

ACE inhibitors and A2RBs have antiproteinuric properties which are independent of their blood pressure lowering effect. Used in combination, these agents can produce more potent reductions in proteinuria. However, there have been concerns about potential adverse effects such as renal failure, hyperkalaemia and hypotension out-weighting these benefits in all except those with refractory proteinuria.47

Direct renin inhibition

More recently, attention has focused on the direct renin inhibitor Aliskerin. It was hoped that this combination of treatment would have additional benefits in terms of lowering proteinuria. However, in the ALTITUDE study of patients with T2DM, ischaemic heart disease and renal impairment treated with Aliskerin in combination with usual therapy was terminated due to an increased risk of CVA, renal failure, hyperkalemia and hypotension in combination therapy group. EMA recommended that Aliskiren is not used in diabetic patients treated with ACEI or A2RB.48

Cardiovascular risk

The relationship between DN and cardiovascular disease is well established. Microalbuminuria is associated with a 2–3-fold increase in cardiovascular risk. In patients with proteinuria, cardiovascular risk is 10 times that of normoalbuminuric patients.49

Therefore, aggressive cardiovascular risk management is vital for all patients with microalbuminuria or DN. Data from the Steno-2 study of patients with T2DM and microalbuminuria demonstrated that intensive multifactorial management of cardiovascular risk factors was associated with a 53% reduction in risk of cardiovascular events and 61% reduced risk of DN after 8 years of follow-up.50 This study demonstrated that the benefits of early aggressive intervention last beyond the end of the period of intervention. When subjects were studied after 13.3 years, there was a 29% absolute risk reduction in cardiovascular events in the intensively treated group and a 20% absolute risk reduction in death from any cause.51

However, a recent meta-analysis by Yudkin et al.52 concluded that intensive glycaemic control is a weaker risk factor than blood pressure or cholesterol lowering. The complexity of glucose lowering therapy (i.e. multiple daily injection doses of insulin, requirement of regular
glucose monitoring, side effect of anti-diabetic medications) and the increased incidences of hypoglycaemia make tight glycaemic control less beneficial. Emerging evidence suggests the primary goal for treating hyperglycaemia in maintaining euglycaemia, but not at the expense of hypoglycaemia. The American Diabetes Association (ADA) and NKF currently recommend an HbA1c target of <7% in most diabetic patients irrespective of stage of CKD.\textsuperscript{53,54} NICE recommends a target HbA1c of <7% for patients with T1DM,\textsuperscript{55} and of 6.5% for patients with T2DM.\textsuperscript{56} However, target HbA1c needs to be individualized according to the anticipated long-term benefit and potential for hypoglycaemia, the NICE guidelines and targets are currently under review.

**Dyslipidaemia**

Studies have unequivocally demonstrated that lipid lowering therapy in patients with T2DM is beneficial. NICE guidelines recommend a therapeutic goal for total cholesterol of 4 mmol/l, an LDL-C concentration <2.0 mmol/l.\textsuperscript{56} If lipid targets are not achieved with lifestyle management, statins are the lipid-lowering agents of choice for patients with CKD stage 1–4. Additional therapy such as fibrates, ezetimibe, niacin or bile acid sequestrant should be considered if the patients do not obtain the lipid goal, with the choice of agent dependent upon clinical circumstances.

**Antithrombotic therapy**

The use of aspirin as a secondary prevention strategy in those with diabetes and existing cardiovascular disease is recommended by all relevant guidelines and is supported by a strong evidence base. However, the use of aspirin for primary prevention of cardiovascular disease in people with diabetes remains equivocal. The ADA\textsuperscript{53} and NICE\textsuperscript{56} recommend the use of low dose aspirin as primary prevention in those with microalbuminuria. Data from meta-analysis studies failed to prove a clear benefit of aspirin in this group.\textsuperscript{57} Physicians should weigh up the benefits and risks of low-dose aspirin in all individuals. An accurate 10-year CVD risk assessment is essential prior to prescribing aspirin for the primary prevention of CVD.\textsuperscript{58}

**Smoking cessation**

Smoking is a strong predictor of renal disease. It is associated with progression of DN in patients with T2DM. Also in patients presenting
with newly diagnosed T2DM, heavy microalbuminuria was more common in smokers than non-smokers.\textsuperscript{59} Smoking cessation is strongly recommended.

**Weight loss**

Obesity is strongly associated with T2DM. These conditions are also associated with an increased incidence of CKD. Weight reduction has positive impact on renal outcomes. Weight loss not only improves glycaemic control but also reduces cardiovascular risk. Target body weight should be individualized to the patient. Life style modification should be first line and anti-obesity medication (Orlistat) should be added if needed. Bariatric surgery being reserved for severely obese patients.

**Dietary modifications**

The ADA recommend limiting protein intake of 0.8 g/kg body weight per day or lower in patients with early CKD.\textsuperscript{53} Adopting the Dietary Approaches to Stop Hypertension diet, reducing sodium intake (<2.4 g/d of sodium or <6 g of salt) and limiting alcohol consumption within normal limit have a positive impact on blood pressure.

**Conclusion**

With the increasing number of patients developing T2DM we will see the inevitable rise in the prevalence of associated complications including the development of microalbuminuria and DN. The evidence demonstrates that these patients are at risk of progressing to ESRD and also at high risk of cardiovascular events. The evidence supports early multifactorial intervention to correct modifiable risk factors and reduce the progression of renal disease and risk of cardiovascular events.

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