Identification and management of diabetic nephropathy

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Abstract

Diabetic kidney disease is the leading cause of end-stage kidney disease in developed countries. It accounts for up to 40% of patients requiring renal replacement therapy. Optimum glycaemic and blood pressure control are currently the only strategies that have shown benefits in both preventing and attenuating the progression of diabetic renal disease. However, recent discoveries of several underlying mechanisms have led to the discovery of novel promising therapeutic agents that have proved to be very effective in several outcomes studies. In particular clinical trials, new antihyperglycaemic agents have demonstrated very promising results, independent of glucose control.

Keywords Albuminuria; chronic kidney disease; diabetic nephropathy; prevention; risk factors

Key points

- The prevention and management of diabetic nephropathy are an increasing worldwide healthcare and health economic challenge
- Multiple modifiable and non-modifiable risk factors are involved in disease progression
- Managing lifestyle changes, hypertension and glycaemic control are key features of the care of individuals with diabetic nephropathy
- Pharmacotherapy for diabetic nephropathy involves many different classes of antihypertensive and antidiabetic medications, but not all are indicated or equally effective in preventing renal progression with established chronic kidney disease
- A personalized approach is therefore needed for the care of individuals with diabetic nephropathy

Introduction

Diabetic nephropathy (DN) is the most common cause of end-stage kidney disease (ESKD) in developed countries, affecting 20–40% of individuals requiring dialysis and/or transplantation. The incidence of DN is also rising at an alarming rate even in developing countries. DN is characterized by: (1) persistent albuminuria (>300 mg/day or >200 microgram/minute) confirmed on at least two occasions 3–6 months apart, (2) a progressive decline in glomerular filtration rate (GFR), and (3) elevated arterial blood pressure.

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The natural history of DN, typified by a progressive increase in albuminuria from normoalbuminuria to overt proteinuria, followed by a declining GFR, has changed profoundly; this is in part because of the effects of treatment. Remission or regression of microalbuminuria (incipient DN) is a common feature of both type 1 (T1DM) and type 2 (T2DM) diabetes mellitus, and is more common than progression to proteinuria. Moreover, a fall in GFR has frequently been seen even in the absence of albuminuria, possibly because of predominant macro- and or microvascular and tubulo-interstitial lesions.

Histological changes in DN are identical in T1DM and T2DM. People with T1DM and T2DM have equivalent rates of proteinuria, azotaemia and ultimately ESKD. The two types of diabetes show strong similarities in rate of renal functional deterioration and onset of co-morbid complications.

Pathophysiology

Nephromegaly, glomerulomegaly and concomitant glomerular hyperfiltration (GFR >150 ml/minute/1.73 m^2) are the initial hallmarks of diabetic kidneys. Glomerular basement membrane thickening and mesangial expansion are early histological lesions, while a progressive depletion of podocytes from either apoptosis or detachment with podocyturia is an early ultrastructural feature. Later, glomerulosclerosis develops with nodules (Kimmelstiel–Wilson lesions) and hyaline deposits in the glomerular arterioles. It has recently been shown that the mesangial expansion and hyalinosis are partly the result of amylin (β-islet-specific amyloid protein) deposits. These later changes are associated with heavy proteinuria. There is a variable degree of concomitant tubular atrophy and interstitial fibrosis, the severity of which, in common with all chronic renal diseases, is a strong predictor of renal survival.

The Renal Pathology Society has developed a consensus classification of diabetic glomerular changes combining type 1 and type 2 DN (Table 1). This discriminates lesions by increasing degree of severity for use in international clinical practice, as highlighted by Figures 1–5 in Table 1.

Risk factors and pathogenesis

Currently, only 20–40% of individuals with T1DM and T2DM ultimately develop DN. This is thought to be a result of associated risks, as outlined in Table 2.

Haemodynamic factors

Glomerular hypertension and hyperfiltration are early manifestations of renal involvement in diabetes mellitus. They result from decreased resistance in both the afferent and efferent arterioles of the glomerulus. Vasodilation is increased to a greater extent in the afferent arteriole than the efferent, resulting in a transmission of systemic blood pressure to the glomerulus. Defective autoregulation is putatively caused by several factors, including prostanoids, nitric oxide, vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1; a potent fibrogenesis cytokine), endothelin and the renin–angiotensin–aldosterone system (RAAS), specifically angiotensin II.

Excessive RAAS upregulation causing efferent vasoconstriction is partly triggered by low sodium delivery to the juxtaglomerular apparatus; this is the result of excessive sodium absorption alongside glucose in the proximal tubules by sodium glucose co-transporters 1 and 2 (SGLT1, SGLT2). Moreover, low sodium delivery to the juxtaglomerular apparatus results in reduced adenosine production because of a reduced requirement for sodium absorption, and hence a decrease in sodium/potassium ATPase activity. As adenosine acts as a vasoconstrictor of the afferent arteriole, relative adenosine deficiency leads to afferent vasodilatation augmenting the glomerular hypertension of RAAS activation.

These early haemodynamic changes promote albumin leakage from the glomerular capillaries and an overproduction of mesangial matrix, as well as thickening of the glomerular basement membrane and injury to podocytes (see Further reading). The preferred use of RAAS blockers in DN, and more recently SGLT2 inhibitors, is justified by the desire to interrupt these detrimental pathways.

Hyperglycaemia

Hyperglycaemia is a crucial factor in the development of DN as demonstrated by its reversal in individuals with T1DM who undergo successful pancreatic transplants (with achievement of normoglycaemia). Hyperglycaemia is associated with an increase in mesangial cell proliferation and hypertrophy, as well as increased matrix production and basement membrane thickening. It may also upregulate VEGF expression in podocytes, resulting in increased vascular permeability.

Five mechanisms have been postulated to explain how hyperglycaemia causes tissue damage; oxidative stress seems to be a theme common to all five. Generally, nephrons produce large amounts of reactive oxygen species that are neutralized by endogenous antioxidant enzymes and free radical scavenging systems. Reactive oxygen species mediate many toxic biological effects, such as peroxidation of cell membrane lipids, oxidation of proteins, renal vasoconstriction and damage to DNA. Hyperglycaemia tips the balance towards the production of reactive oxygen species, most of which seem to be generated within or by mitochondria. The five mechanisms are outlined below.

First, non-enzymatic glycosylation generates advanced glycosylation end products (AGEs), which accumulate to contribute to the associated renal and microvascular complications. AGEs interact with AGE receptors to cause reduced nitric oxide generation in a dose-dependent manner.

Second, activation of protein kinase C leads to increased secretion of vasodilatory prostanoids, which contribute to glomerular hyperfiltration. By activating TGF-β1, protein kinase C might also increase the production of extracellular matrix by mesangial cells.

Third, there is an acceleration of the aldose reductase pathway, resulting in an accumulation of sorbitol in the tissue. Several lines of research are in progress to develop specific and selective inhibitors of these pathways, downstream of hyperglycaemia. Current practice, however, is to achieve optimum glycaemic control in patients with DN.

Fourth, there is activation of cytokines, pro-fibrotic elements, inflammation and dysregulated vascular growth factors such as VEGF, which causes excessive matrix accumulation, a hallmark of DN. Hyperglycaemia also increases the expression of TGF-β1 and inflammatory cytokines, specifically interleukin (IL)-1, IL-6, IL-18 and tumour necrosis factor: these contribute to the development and progression of DN. Concentrations of these cytokines are increased in serum and urine and correlate with the progression of nephropathy, indicated by increased urinary albumin excretion.

Finally, in order to maintain a dynamic functional barrier, podocytes must possess an adequate amount of nephrin, a slit diaphragm protein. Individuals with DN have markedly reduced renal nephrin expression and fewer electron-dense slit diaphragms, when compared with those without diabetes mellitus but with minimal-change disease, or with controls. Furthermore, nephrin excretion is raised up to 17–30% in individuals with diabetes mellitus (with or without albuminuria) compared with those without diabetes. Thus, nephrin excretion could be an early finding of podocyte injury, even before the onset of albuminuria. It has been suggested that treatment with RAAS blockers might help protect nephrin expression.

Genetic susceptibility

Genetic factors appear to play an important role in the incidence and severity of DN. The risk of DN cannot be explained entirely by the duration of diabetes mellitus or hypertension, or the degree of glycaemic control. Environmental and genetic factors have complementary roles in the pathogenesis of DN, and the likelihood of developing DN is markedly increased in those who have a sibling or parent with DN.

Advances in molecular genetics have led to the identification of many DN susceptibility gene variants on many chromosome loci. There is a higher prevalence of diabetes mellitus and incidence of DN in certain ethnic groups such as South Asian, African ancestry, Pima Indian and Aboriginal populations; this is also determined partly by genetic variants, but more importantly by an epigenetic alteration of DNA and expression of non-coding microRNA. Our understanding of the epigenome is still in its infancy.

ACE gene polymorphism has been explored in several studies. The insertion–deletion polymorphism is responsible for

Renal Pathology Society Classification of type 1 and 2 DN[1]

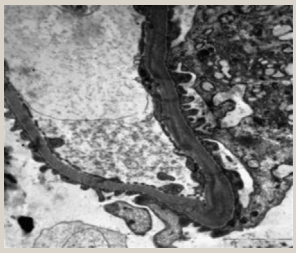
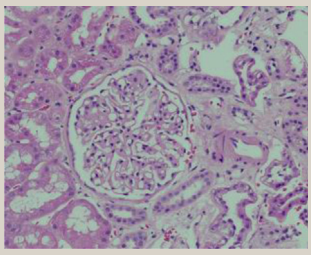
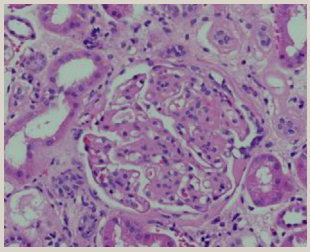
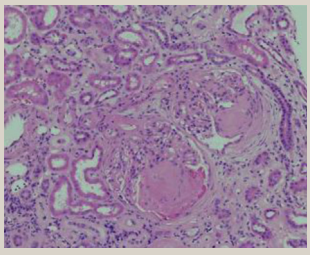
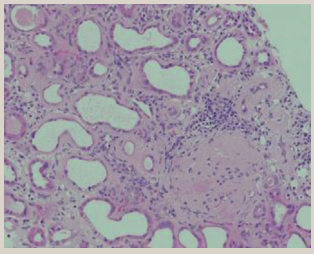
Class	Name	Histology
I	Isolated glomerular basement membrane thickening (>395 nm in female patients, >430 nm in males). No evidence of mesangial expansion, mesangial matrix increase, or global glomerulosclerosis involving >50% of the glomeruli	
		Figure 1 Electron microscopy showing a thickened glomerular basement membrane
IIa	Mild mesangial expansion	
		Figure 2
IIb	Severe mesangial expansion (in severe lesions, >25% of the total mesangium contains areas of expansion larger than the mean area of a capillary lumen)	
		Figure 3
III	Nodular intercapillary glomerulosclerosis (≥1 Kimmelstiel–Wilson lesions) and <50% global glomerulosclerosis	
		Figure 4
IV	Advanced diabetic glomerulosclerosis and >50% global glomerulosclerosis	
		Figure 5

Table 1

Risk factors that contribute to development of DN

Non-modifiable	Modifiable
Ethnicity	Glycaemia
Genetic susceptibility	Hypertension
Elevated estimated GFR	Smoking
Reduced estimated GFR	Dyslipidaemia
Retinopathy	Obesity

Table 2

individual differences in plasma concentrations of angiotensin-converting enzyme (ACE). In those with diabetes, the DD polymorphism of the *ACE* gene has been associated with an increased risk of developing DN, severe proteinuria, progressive renal failure and mortality during dialysis. Other studies have, however, produced conflicting data. It is more likely that *ACE* polymorphism is associated with the progression of DN and has no direct role in its development.

Diagnosis and screening

Urine albumin excretion in healthy adults is <20 mg/day, or a urine albumin:creatinine ratio (uACR) <3 mg/mmol; any other persistent value is considered abnormal. Albumin is the preferred protein as it is highly sensitive to glomerular permeability, and large fluctuations in albumin excretion can be detected even when there is no significant amount of total proteinuria; this is possibly because of impaired albumin absorption in the brush border of the proximal tubule in the diabetic milieu. However, an abnormal ACR can also be a result of urinary tract infection, fever, physical exercise or posture. Hence it is important to repeat the test for an abnormal uACR 3 months after the initial test. An early morning urine sample is preferred, as a variation in albumin excretion has been reported throughout the day. Annual screening is advised in any individual with T1DM after 5 years of diagnosis, or earlier if there is evidence of poor glycaemic control. Individuals with T2DM are advised to undergo yearly surveillance from the point of diagnosis.

Microalbuminuria (urinary albuminuria 20–300 mg/day) usually develops 10–15 years after the onset of diabetes mellitus, followed by macroalbuminuria (urinary albuminuria >300 mg/day). This is classically seen in T1DM but less often in T2DM. An assessment of renal function in the form of an estimated GFR (eGFR) would help stage chronic kidney disease (CKD) in the presence of an abnormal albumin excretion rate. Not all diabetic individuals with microalbuminuria progress to macroalbuminuria, and regression to normoalbuminuria has been reported in several studies. In T2DM, it is common to see patients with renal impairment but without albuminuria. This is likely to be caused by medications with alleged antiproteinuric properties, as such individuals would already be taking these drugs for other co-morbidities.

Patients can be classified according to CKD staging, based on both GFR and uACR quantification, with GFR stages split into six categories: G1, >90 ml/minute/1.73 m^2; G2, 60–89 ml/minute/1.73 m^2; G3A, 45–59 ml/minute/1.73 m^2; G3B, 30–44 ml/minute/1.73 m^2; G4, 15–29 ml/minute/1.73 m^2; and G5 <15 ml/minute/1.73 m^2. In addition, uACR values can be split into three categories: A1, <3 mg/mmol; A2, 3–30 mg/mmol; and A3, >30 mg/mmol. Thus a patient with a GFR of 32 ml/minute/1.73 m^2 and a uACR of 23 mg/mmol would be classified as having CKD G3B A2.

Indications for biopsy

The diagnosis of DN is usually made by a clinical assessment of risk factors, resulting in a presumptive diagnosis, and generally avoiding the need for renal biopsy (Table 3).

Treatment

Lifestyle changes

Cessation of smoking, an increase in exercise, weight loss, a healthy diet, oral salt restriction, blood pressure control, poor metabolic regulation and hyperlipidaemia should be addressed in every individual with diabetes. Dietary advice should focus on heart-healthy foods with enough fruit, vegetables, whole grains, low-fat dairy products, poultry, fish and nuts, or on Mediterranean-style diets. The glycaemic index is a useful physiological concept for describing the effect on blood glucose of different carbohydrates, but it appears to have little clinical value. However, patient education on salt restriction (5–6 g/day) should be a priority because this not only has primary benefits, but can also secondarily potentiate the effectiveness of RAAS blockers, which play a pivotal role in ameliorating the severity of DN.

The American Diabetes Association advocates a low-protein diet. A recent meta-analysis of 13 randomized controlled trials involving 779 individuals with T1DM and T2DM found that a low-protein diet was associated with a significant improvement in GFR. A low protein intake is defined as 0.6 g/kg body weight per day.

Glycaemic control

Optimal glycaemic control – glycated haemoglobin (HbA_{1c}) <53 mmol/mol (<7%) can slow the progression of DN. In the Diabetes Control and Complications Trial (DCCT), 1365 individuals with T1DM and normoalbuminuria randomized to the intensive glucose control group had a lower incidence of microalbuminuria and macroalbuminuria after 10 years of follow-up (see Further reading). This was also supported by the United Kingdom Prospective Diabetes Study (UKPDS) of T2DM

Indications for renal biopsy in patients with suspected DN

- Absence of microvascular complications
- Active urinary sediment
- Non-visible haematuria
- Rapid-onset proteinuria
- Suspicion of other underlying glomerular/tubular pathology with abnormal complement
- Rapid decline in renal function with no cause identified
- Short duration of T1DM

Table 3

that revealed a 25% reduction in microvascular complications and a 6% reduction in all-cause mortality (see Further reading). The suggested target HbA_{1c} was set at around 53 mmol/mol (7%) to avoid hypoglycaemic episodes.

The ADVANCE and ACCORD trials compared more intensive glucose control (target HbA_{1c} values ≤47 mmol/mol (≤6.5%) and ≤42 mmol/mol (≤6.0%) respectively) with standard glucose control (defined by local guidelines or HbA_{1c} values of 53 −63 mmol/mol (7.0−7.9%)). In 2008, the primary results of the trials challenged the benefits of more intensive glycaemic control in this population compared with the targets used in the DCCT and UKPDS (see Further reading). New findings from a 6-year follow-up evaluation of the surviving ADVANCE trial participants (ADVANCE-ON) and a *post hoc* analysis of the ACCORD data have provided further evidence that more intensive glucose control might not be beneficial in patients with T2DM, particularly those with CKD.[2,3]

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines currently recommend an $HbA1_c$ target of around 53 mmol/mol (7.0%) to prevent or retard the progression of diabetic microvascular complications, including CKD. This recommendation is consistent with the ACCORD data, which suggest that, in individuals with T2DM and impaired renal function, HbA_{1c} concentrations should be targeted to 53 mmol/mol (7%) to avoid excess mortality. Alleged borderline reno-protective effects of a lower glycaemic target are supported by the ADVANCE and ADVANCE-ON studies, suggesting that reno−protection may require more intensive glycaemic control. However, the absolute reduction in risk of ESKD with this strategy was minimal: the overall event rate of ESKD was <1% and did not translate into a detectable effect on mortality.

Considering the adverse effects on cardiovascular and all-cause mortality observed in the ACCORD study, there has been a move towards an individualization of glycaemic targets depending on additional co-morbidities. In patients with a long disease duration, shorter life expectancy, multiple co-morbidities, established vascular complications, patient preference for less monitoring and resource challenges, a less intensive approach to glycaemic targets may be warranted.

Hypertension

Hypertension is a well-known risk factor for the onset of DN and progression of disease. In T2DM, hypertension is also a powerful predictor of cardiovascular death, increasing the risk by a factor of 20. The 2021 KDIGO clinical guidelines for the management of blood pressure in CKD advocate a target systolic blood pressure of <120 mmHg, regardless of the presence of diabetes. For individuals with diabetes, it is recommended that this target should be preferably achieved with RAAS blockade. The American Diabetes Association recommendation in 2020 similarly suggests that:

- individuals with T1DM with hypertension and albuminuria should be started on ACE inhibitors
- individuals with T2DM, hypertension and microalbuminuria should be given ACE inhibitors or angiotensin receptor blockers (ARBs)
- T2DM associated with hypertension and overt nephropathy should be treated with ARBs.

When a particular choice of RAAS blockade agent is not tolerated, it should be substituted by another drug with a similar action.

Antihypertensive agents

ACE inhibitors: there has been good evidence since the early 1990s regarding the antiproteinuric effect of ACE inhibitors. The Collaborative Study Group trial of 409 type 1 diabetic individuals showed that captopril treatment reduced the risk of doubling of serum creatinine by 48% and reduced the composite outcome of death, dialysis and transplantation by 50% compared with placebo. This study also demonstrated that a sustained remission of nephrotic range proteinuria was possible with ACE inhibitors. The ADVANCE trial showed that the combination of perindopril and indapamide treatment reduced new-onset macroalbuminuria and prevented the progression of microalbuminuria to overt nephropathy. Finally, the BENEDICT study showed that ACE inhibitor treatment could delay the onset of microalbuminuria in type 2 diabetic individuals with hypertension and baseline normoalbuminuria.

ARBs: in the Irbesartan Diabetic Nephropathy Trial, irbesartan reduced the risk of ESKD or doubling of serum creatinine by 20 −23% compared with amlodipine or placebo. This was a randomized controlled trial in type 2 diabetic individuals with nephropathy. In the RENAAL trial, involving 1513 type 2 diabetic individuals with nephropathy, losartan reduced the risk of ESKD or doubling of serum creatinine by 25−28% compared with placebo. The ROADMAP trial of 4447 individuals with T2DM demonstrated that olmesartan was effective in delaying the onset of microalbuminuria; however, the mean blood pressure was lower, leading to an increased rate of cardiovascular events in those with pre-existing ischaemic heart disease. This highlights the importance of caution in striving for intensive blood pressure targets in individuals who have DN and coexistent ischaemic heart disease.

When starting an ACE inhibitor or ARB, the GFR should be monitored 2−4 weeks later. A fall in eGFR of up to 30% can be expected. If there is a rise of >30%, there should be a review for causes of AKI: volume depletion should be corrected if present, concomitant medications (e.g. non-steroidal anti-inflammatory drugs) assessed and renal artery stenosis considered. If mitigation strategies are ineffective, consider reducing or stopping the ACE or ARB.

ACE inhibitors versus ARBs: one of the mainstays of effectively slowing the progression of DN is an ACE inhibitor or ARB. Very few data are available on the initiation of ARBs in T1DM. In one study in 250 individuals with T2DM and early DN, there was no difference in the rate of decline of GFR between the telmisartan and enalapril groups over 5 years. In a meta-analysis of eight studies for the primary prevention of DN, ACE inhibitors reduced the risk of new-onset microalbuminuria, macroalbuminuria or both in comparison to placebo. However, similar benefits could not be demonstrated for ARBs. Notably putative specific reno-protective effects of ACE inhibitors when compared against another antihypertensive agent with an equivalent degree of blood pressure control are not seen, indicating that ACE inhibitors and ARBs are just good antihypertensive agents.

Currently, neither ACE inhibitors nor ARBs are recommended in normotensive and normoalbuminuric patients with diabetes mellitus for the primary prevention of DN.

Combinations of ACE inhibitors and ARBs: combination therapy with an ACE inhibitor and ARB was previously used as this was considered superior to single-agent therapy in lowering albuminuria and blood pressure. However, the ONTARGET trial, which included diabetic patients with a high risk of vascular disease without renal impairment, showed no significant difference in the incidence of dialysis or doubling of serum creatinine compared with single-agent use for RAAS blockade.[4] Combined RAAS blockade led to more adverse events without additional benefit, and either drug alone was equally effective in preventing the combined primary outcome. Similarly, when tried even in patients with established DN, the combined use of ACE inhibitors and ARBs/renin inhibitors did not provide an additional benefit but was associated with an increased risk of acute kidney injury and hyperkalaemia. This strategy is therefore no longer recommended.[4]

Unlike other types of kidney disease, such as pyelonephritis, renal stones and vasculitis, most renal injury in diabetes mellitus is clinically occult. The timing of medical intervention during this silent phase is reno-protective, as judged by the attenuated loss of GFR. Despite intensified metabolic control and antihypertension treatment in individuals with diabetes, a substantial number still go on to develop ESKD, which has led to an intense search for novel strategies to halt the development and progression of DN amidst the growing epidemic of diabetes mellitus.

Finerenone, a non-steroidal selective mineralocorticoid receptor antagonist, was effective in patients with established DN who were taking the maximal tolerated dose of an ACE inhibitor or ARB. Treatment with finerenone resulted in a reduction in the composite outcome (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline or death from renal causes) by 27% compared with placebo. Despite a modestly increased risk of hyperkalaemia with finerenone (2.3%) compared with placebo (0.9%), finerenone was well tolerated and is in the process of approval by national regulatory bodies.

Atrasentan, a selective endothelin A receptor antagonist, has been generally safe and effective in reducing residual albuminuria when used in individuals with DN who are already being given stable doses of RAAS blockers. In a recent multicentre placebo-controlled trial of >2000 patients with established diabetic kidney disease, 0.75 mg daily of atrasentan was associated with a significantly lower risk of renal outcomes (a doubling of creatinine and/or ERKD) of 6.0% compared with placebo (7.9%) after 2.2 years of follow-up. There were differences in cardiac safety endpoints. Atrasentan will hopefully find its use as an adjuvant to SGLT2 inhibitors in the pharmacological arsenal.

Novel antihyperglycaemic agents

Glucagon-like peptide 1 receptor agonists (GLP1RAs) and SGLT2 inhibitors have emerged as two new classes of antihyperglycaemic agent for individuals with T2DM that also reduce cardiovascular risk and possibly progression of kidney disease. In a systematic review and trial-level meta-analysis of GLP1RA and SGLT2 inhibitor cardiovascular and renal outcome trials, GLP1RAs and SGLT2 inhibitors reduced atherosclerotic major cardiovascular events to a similar degree in individuals with established atherosclerotic cardiovascular disease, whereas SGLT2 inhibitors had a more marked effect on preventing heart failure and progression of kidney disease. Their distinct clinical benefit profiles should be considered in the decision-making process when treating patients with T2DM for additional cardio-renal protection in addition to their antihyperglycaemic actions. The astonishing success of SGLT2 inhibitors has resulted in their adoption as first-line therapy in addition to RAAS blockade at all stages of DN.[5]

Recommendations

DN and ESKD remain a significant clinical problem. In diabetic individuals in whom no single treatment is able to halt progression of DN, a multidisciplinary approach delivered by a multiprofessional team remains the most sensible strategy. The main goals are reno-protection and optimization of treatment, as outlined below.

Reno-protection in DN – targets:

- systolic blood pressure <120 mmHg
- proteinuria <0.5 g/24 hours
- HbA_{1c} around 53 mmol/mol (7%).

Treatment for patients with DN and proteinuria >1 g/day:

- ACE inhibitors or ARBs: uptitrate to maximum dose (in T2DM, ARBs are preferable)
- avoidance of using dual ACE inhibitors, ARB and renin blockers in an individual patient except in exceptional circumstances
- restriction of salt intake and addition of a diuretic to prevent hyperkalaemia and potentiate the antihypertensive effects of RAS blockers
- addition of SGLT2 inhibitors according to individual licence unless specifically contraindicated (i.e. a history of recurrent diabetic ketoacidosis)
- addition of a calcium channel blocker (preferably verapamil or diltiazem) if goals have not been achieved.

Additional measures:

- statins and, if needed, ezetimibe or fibrates to lower total cholesterol to <4 mmol/litre
- stop smoking (as smoking produces a 3-fold higher rate of deterioration of CKD)
- a modestly protein-restricted diet (0.6 g/kg body weight)
- salt restriction to 5–6 g/day, and promotion of exercise and a healthy diet.

An appropriate and timely referral to specialist services is advisable. According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines, a nephrology referral should be considered if any of the following are present:

- eGFR <30 ml/minute/1.73 m^2 at diagnosis
- worsening proteinuria despite treatment
- loss of GFR of >1 ml/minute/1.73 m^2 per month
- active urinary sediment
- absence of retinopathy
- >30% reduction in eGFR after starting an ACE inhibitor or ARB
- refractory hypertension
- another suspected cause of renal disease, for example connective tissue disease. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 45-year-old woman presented with frothy urine. She had a 5-year history of hypertension, and a 4-year history of type 2 diabetes mellitus. She was an ex-smoker with a 10 pack–year history and had a family history of type 2 diabetes mellitus. She was taking amlodipine and metformin.
On clinical examination, there was ankle oedema, and bilateral microaneurysms and cotton wool spots were seen on fundoscopy. The examination was otherwise unremarkable. Blood pressure was 152/87 mmHg. Urine dipstick showed glucose 2+, blood 2+ and protein 3+.

Investigations

- Estimated glomerular filtration rate 45 ml/minute/1.73 m^2 (>60)
- HbA_{1c} 60 mmol/mol (<42); 7.6% (<6%)
- Urine protein:creatinine ratio 387 mg/mmol (<30)

She then underwent a renal biopsy.

What is the most likely histological finding on light microscopy of the biopsy specimen?

A. Normal renal biopsy
B. Diffuse mesangial matrix expansion with intercapillary nodules
C. Thickening of the basement membrane
D. Widespread scarring
E. Widespread glomerular microthrombi

Question 2

A 45-year-old man presented with newly diagnosed chronic kidney disease. He had a 20-year history of type 1 diabetes mellitus.

What is the most important dietary advice that he should be given?

A. Restrict protein intake
B. Increase salt intake
C. Low-carbohydrate diet
D. High-fat diet
E. Reduce total calories

Question 3

A 75-year-old man presented with symptomatic heart failure. He had a 17-year history of type 2 diabetes mellitus. He was taking metformin 500 mg once daily and ramipril 2.5 mg once daily.

Investigations

- HbA_{1c} 62 mmol/mol (<42); 7.8% (<6%)
- Estimated glomerular filtration rate 49 ml/minute/1.73 m^2 (<60)
- Blood pressure 118/68 mmHg

What would be the best next step in their treatment regimen?

A. Increase the metformin dose to 500 mg 12-hourly
B. Start an sodium glucose co-transporter 2 (SGLT2) inhibitor
C. Start a glucagon-like peptide 1 receptor agonists (GLP1RA)
D. Optimize the angiotensin-converting enzyme inhibitor (ACEi)
E. Add in a loop diuretic