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 prevention and attenuation of the progression of diabetic renal disease. However, recent discoveries of several underlying mechanisms have led to the discovery of novel promising therapeutic targets awaiting outcomes studies. In ongoing outcome trials, new antihyperglycaemic agents in particular have demonstrated very promising results independent of glucose control.

Keywords Albuminuria; chronic kidney disease; diabetic nephropathy; MRCP; 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 patients 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 patients with diabetic nephropathy

Introduction

Diabetic nephropathy (DN) is the most common cause of end-stage kidney disease (ESKD) in developed countries, affecting 20–40% patients 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.

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, 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) are the initial hallmarks of diabetic kidneys. Glomerular basement membrane thickening and mesangial expansion are early histological lesions, while 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.

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

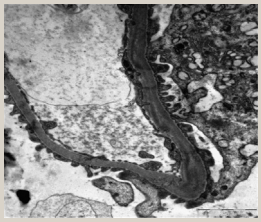
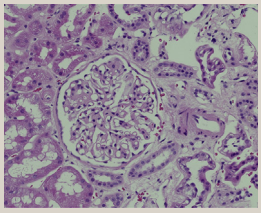
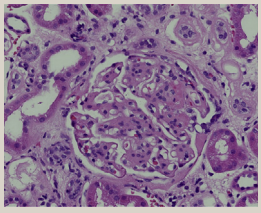
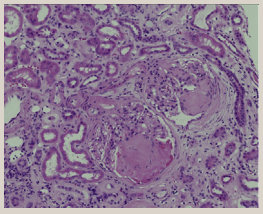
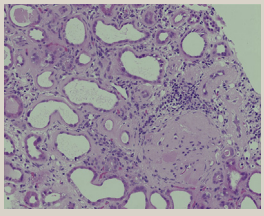
Class	Name	Histology
I	Isolated glomerular basement membrane thickening (>395 nm in female patients, >430 nm in males). No evidence of mesangial expansion, mesangial matrix increase or global glomerulosclerosis involving >50% of the glomeruli	 **Figure 1** Electron microscopy showing a thickened glomerular basement membrane
IIa	Mild mesangial expansion	 **Figure 2**
IIb	Severe mesangial expansion (in a severe lesion, >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 lesion(s)) 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

Risk factors and pathogenesis

Currently only 20–40% of patients 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 decreased to 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), endothelin, and the renin–angiotensin–aldosterone system (RAAS), specifically angiotensin II. Excessive RAAS upregulation is partly triggered by low sodium delivery to the juxtaglomerular apparatus as a result of excessive sodium absorption alongside glucose in the proximal tubules by sodium glucose co-transporters 1 and 2 (SGLT1, SGLT2). These early haemodynamic changes promote albumin leakage from the glomerular capillaries and 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 and more recently SGLT2 blockers in DN is justified by the desire to interrupt these detrimental pathways.

Hyperglycaemia

Hyperglycaemia is a crucial factor in the development of DN as it can be reversed by successful pancreatic transplants (with achievement of normoglycaemia) in type 1 diabetic patients. Hyperglycaemia is associated with an increase in mesangial cell proliferation and hypertrophy, as well as increased matrix production and basement membrane thickening. It might 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, the nephron produces a large amount 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 the AGE receptor (RAGE), to cause reduced nitric oxide generation in a dose-dependent manner.

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

Third, there is an acceleration of the aldose reductase pathway, resulting in 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 is, however, 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 (TNF), which 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, podocytes with an adequate amount of nephrin, a slit diaphragm protein, are important for maintaining the dynamic functional barrier. Patients with DN have markedly reduced renal nephrin expression and fewer electron-dense slit diaphragms compared with patients without diabetes mellitus and with minimal change disease, or with controls. Furthermore, nephrin excretion is raised up to 17–30% in patients with diabetes mellitus (with or without albuminuria) compared with individuals without diabetes. Thus, nephrin excretion could be an early finding of podocyte injury, even before the onset of albuminuria. Treatment with RAAS blockers might help to protect nephrin expression (see Further reading).

Genetic susceptibility

Genetic factors seem 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. The higher prevalence of diabetes mellitus and incidence of DN in certain ethnic groups such as South Asian, Black, Pima Indian and Aboriginal populations is also determined partly by genetic variants, but more importantly by epigenetic alteration of DNA and expression of non-coding microRNA. Our understanding of the epigenome is still in its infancy.

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 complements
- Rapid decline in renal function with no cause identified
- Short duration of type 1 diabetes mellitus

Table 3

ACE gene polymorphism has been explored in several studies. The insertion–deletion polymorphism is responsible for the difference in plasma levels of angiotensin-converting enzyme (ACE) between individuals. In patients 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* gene polymorphism is associated with the progression of DN and has no direct role in its development.

Diagnosis and screening

Urine albumin:creatinine ratio (ACR) is normally 0–20 mg/day, and any other concentration 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 fever, heart failure, physical exercise or posture. Hence it is important to repeat the test for an abnormal urine ACR within 3 months of the initial test. An early morning urine sample is preferred, as variation in albumin excretion has been reported throughout the day. 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 uACR. 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.

Indications for biopsy

The diagnosis of DN is usually made by 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, increase in exercise, weight loss, a healthy diet, oral salt restriction, blood pressure control, poor metabolic regulation and hyperlipidaemia should be addressed in every diabetic individual. 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 renin–angiotensin system (RAS) 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/day.

Glycaemic control

Optimal glycaemic control measured using 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 were 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 that revealed a 25% reduction in microvascular complications and 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 Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials compared more intensive (target HbA_{1c} levels <48 mmol/mol (≤6.5%) and <42 mmol/mol (≤6%), respectively) with standard glucose control (as defined by local guidelines or HbA_{1c} 53–63 mmol/mol (7.0–7.9%), respectively). 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 now provided further evidence that more intensive glucose control might not be beneficial in patients with T2DM, particularly in 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%) to prevent or retard the progression of diabetic

microvascular complications, including CKD. This recommendation is consistent with the ACCORD data, which suggest that in patients with T2DM and impaired renal function, HbA_{1c} levels 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 end stage renal disease 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, intensive glycaemic control (HbA_{1c} <48 mmol/mol (≤6.5%)) is not warranted in patients with T2DM and CKD.

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 current consensus by the National Kidney Foundation for diabetic patients with CKD is a target blood pressure of <130/80 mmHg or lower in the presence of overt nephropathy. The 2012 KDIGO recommendations also advocates the same guideline and should be preferably achieved with RAS blockade. The American Diabetes Association recommendation in 2012 suggests the following:

- 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 RAS blockade is not tolerated, it should be substituted by another drug with a similar action.

Antihypertensive agents

ACE inhibitors: there has been good evidence since early 1990s regarding the antiproteinuric effect of ACE inhibitors. In 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 progression of microalbuminuria to overt nephropathy. Finally, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) 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 control trial in type 2 diabetic individuals with nephropathy. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial consisting of 1513 type 2 diabetic patients with nephropathy, losartan reduced the risk of ESKD or doubling of serum creatinine by 25−28% compared with placebo. The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial of 4447 type 2 diabetic patients demonstrated that olmesartan was effective in delaying the onset of microalbuminuria, but 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 blood pressure targets in patients with DN and coexistent ischaemic heart disease.

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, 250 patients with T2DM and early DN showed no difference in 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 primary prevention of DN.

Combinations of ACE inhibitors and ARBs: combination therapy with an ACE inhibitor and an ARB was previously used as this was considered to be superior to single-agent therapy in lowering albuminuria and blood pressure. However, the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), 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 RAS blockade.[4] Combined RAS 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 additional benefit but was associated with 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 patients 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.

Novel therapies

Glucagon-like peptide 1 receptor agonists (GLP1-RAs) and SGLT2 inhibitors have emerged as two new classes of anti-hyperglycaemic agent that also reduce cardiovascular risk and progression of kidney disease. In a systematic review and trial-level meta-analysis of GLP1-RA and SGLT2 inhibitor cardiovascular outcome trials, GLP1-RAs and SGLT2 inhibitors reduced atherosclerotic major cardiovascular events to a similar degree in patients with established atherosclerotic cardiovascular disease, whereas SGLT2 inhibitors have a more marked effect on preventing heart failure and progression of kidney disease. Their distinct clinical benefit profiles are being considered in the decision-making process when treating patients with T2DM for additional cardio-renal protection in addition to their anti-hyperglycaemic actions.[5]

Bardoxolone methyl is a nuclear 1 factor (erythroid-derived 2) −related factor 2 (NRF-2) activator with known antioxidant and anti-inflammatory properties. After the promising results of this agent in a Phase II trial, a large outcome study failed to demonstrate a risk reduction in ESKD or death from cardiovascular causes in patients with T2DM and CKD. However a higher rate of cardiovascular events was noted with bardoxolone methyl compared with placebo, and the trial was terminated prematurely on safety grounds. It is generally believed that bardoxolone is a less specific NRF-2 agonist and is beneficial in patients without overt cardiovascular diseases.

In a recent study, pentoxyphylline (previously used for peripheral vascular disease) was found to slow the rate of decline of eGFR and proteinuria by putatively reducing the production of TNF-α. This interesting observation about a cheap and already used drug is confirmed in large validation studies and could have an immediate global impact.

Similarly, atrasentan, a selective endothelin A receptor antagonist, was generally safe and effective in reducing residual albuminuria when used in individuals with DN already being given stable doses of RAS blockers. This could ultimately translate into improved renal outcomes in patients with T2DM with DN, but this preliminary finding requires confirmation in long-term follow-up studies.

AGE inhibitors reduce AGE formation, enhance degradation or break AGE cross-links. However, two such agents (pimegadine, pyridoxamine) that were effective in pre-clinical models did not show any benefit in randomized controlled clinical trials.

Ruboxistaurin is a selective PKC-β inhibitor. Despite showing promising results in animal models, a recent pooled analysis of three trials of diabetic retinopathy ($n = 1157$) failed to demonstrate reno-protection over a 3-year follow-up period. Aldose reductase inhibitors suppress sorbitol accumulation in tissues. A post hoc analysis of the Aldose Reductase Inhibitor−Diabetes Complications Trial concluded that progression of retinopathy/albuminuria was significantly inhibited by epalrestat. This was a re-analysis of the original 3-year, open-label trial using a subset of patients for whom data were available. However, another inhibitor − ponalrestat − did not affect urinary albumin excretion or glomerular filtration in individuals with T1DM.

In a randomized controlled trial, the addition of paricalcitol (a selective activator of the vitamin D receptor) to treatment with ACE inhibitors reduced albuminuria (a surrogate marker of progressive renal disease) in patients with T2DM. Paricalcitol worked best in individuals with a high dietary sodium intake, a group known to respond poorly to ACE inhibitors and ARB therapy. These promising results await validation in a large outcome trial.

Despite the fact that only modest success has been seen with novel therapies as an adjuvant to current struggles, the quest for new drugs to conquer this devastating condition is, reassuringly, continuing.

Despite the fact that only signficant success has been seen with novel therapies as an adjuvant to current strategies, the quest for new drugs to conquer this devastating condition is reassuringly continuing.

Multidisciplinary approach to management

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***
  - Blood pressure <130/80 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 increasing to maximum dose (in T2DM, ARBs are preferable)
  - Avoid using dual ACE inhibitors, ARB and renin blockers in an individual patient except in exceptional circumstances
  - Restrict salt intake and add a diuretic in order to prevent hyperkalaemia and potentiate the antihypertensive effects of RAS blockers
  - Add 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 cholesterol to <4 mmol/litre
  - Stopping smoking (which produces a 3-fold higher rate of deterioration in CKD)
  - Modestly protein-restricted diet (0.6 g/kg body weight)
  - Salt restriction to 5−6 g/day, and promotion of exercise and healthy diet.

An appropriate and timely referral to specialist services is advisable. According to the National Kidney Foundation KDOQI guidelines, a nephrology referral should be considered for:

- eGFR <30 ml/minute at diagnosis
- worsening proteinuria despite treatment
- loss of GFR of >1 ml/minute per month
- active urinary sediments
- 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 for review. She was asymptomatic. She had a 8-year history of type 1 diabetes, well controlled on insulin.
Clinical examination was unremarkable. Urine dipstick was negative for glucose and protein.

Investigations

- HbA_{1c} 40 mmol/mol (20–42)
- Estimated glomerular filtration rate (eGFR) 75 ml/minute (70–140)
- Urinary albumin:creatinine ratio 4.9 mg/mmol (<3.5)

What is the most likely histological change in the kidney at this stage?

A. Minimal change
B. Mesangial matrix expansion
C. Thickening of the basement membrane
D. Hyaline droplets
E. Kimmelstiel-Wilson nodules

Question 2

You meet a patient on the renal ward round with diabetes and an eGFR of 55 ml/minute, who asks you about their diet.

What would your advice be?

A. High protein > 1 g/kg body weight
B. Low potassium diet
C. High salt intake
D. Low salt intake 3–5 g/day
E. Low carbohydrate and high fat diet

Question 3

A 67-year-old man presented for review. He had a 20-year history of type 2 diabetes mellitus. He had also recently been found to have left ventricular failure caused by ischaemic heart disease and had an eGFR of 55 ml/minute. He was taking a loop diuretic, an angiotensin-converting inhibitor and metformin but remained symptomatic from the left ventricular failure. Repeated HbA_{1c} readings were suboptimal.

Which additional class of drug might be expected to improve both the heart failure and the glycaemic control?

A. Sodium-glucose co-transporter type 2 (SGLT2) inhibitor
B. Angiotensin receptor blocker
C. DPP4 inhibitor
D. Thiazolidinedione
E. Spironolactone