# RENOPROTECTION IN DIABETES MELLITUS

*End-stage renal disease is a common and important complication of diabetes.*

**IKECHI G OKPECHI,** ***MB BS, FWACP, PhD, Cert Nephrol (SA) Phys***

***Physician and Nephrologist, Division of Nephrology, Department of Medicine, Groote Schuur Hospital and University of Cape Town***

*Dr Okpechi is originally from Nigeria and completed his PhD at UCT. His research interests are varied, but he concentrates mainly on the genetics of kidney disease in Africa.*

**CHARLES R SWANEPOEL,** ***MB ChB, MRCP (UK), FRCP (Edin)***

***Consultant Nephrologist, Division of Nephrology, Department of Medicine, Groote Schuur Hospital and University of Cape Town***

*Associate Professor Swanepoel graduated from UCT and soon thereafter trained as a nephrologist at the Leeds General Infirmary, University of Leeds Teaching Hospital, UK. On his return to Cape Town, he joined the Department of Medicine at UCT, ultimately being appointed full-time to the Division of Nephrology at Groote Schuur Hospital.*

*Correspondence to: C Swanepoel (Charles.Swanepoel@uct.ac.za)*

Data from developed countries have shown monumental increases in the incidence of end-stage renal disease (ESRD) in patients with diabetes mellitus (DM) (Table I).[1] In response to the increasing threat of the growing prevalence of diabetic nephropathy (DN), several large organisations and expert bodies (i.e. the International Society of Nephrology and the International Diabetes Federation) have put in place programmes that emphasise the importance of early detection of DN. This article focuses on key mechanisms in the pathogenesis of DN and concentrate on the traditional and novel therapies that prevent overt renal disease in DM.

**Table I. Incidence of end-stage renal failure in patients with diabetes[2]**

| | Number of cases/million population/year | |
|---|---|---|
| **Country** | **1984** | **1994** |
| USA | 29.2 | 107.0 |
| Japan | 23.4 | 66.0 |
| Australia | 4.0 | 14.0 |
| Norway | 6.5 | 15.4 (11.1) |
| Germany (South-west) | - | 52.0 (47.0) |
| Italy (Lombardy) | 6.5 (2.9) | 13.0 (7.0) |

Data in parentheses represent number of cases ascribed to T2DM alone.

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## Pathophysiology of renal disease in diabetes

DN is characterised clinically by increasing albuminuria and a decline in renal function. The classic histological changes are the following: an excessive build-up of extracellular matrix (ECM), thickening of glomerular and tubular basement membranes and an increased amount of mesangial matrix (produced by mesangial cells), ultimately progressing to glomerulosclerosis (Kimmelstiel-Wilson nodules) and tubulo-interstitial fibrosis (Fig. 1). In susceptible diabetics, hyperglycaemia targets all types of renal cells and activates various cellular pathways that cause DN through increased activity of growth factors, such as transforming growth factor-β (TGF-β); activation of protein kinase C (PKC); activation of cytokines; formation of reactive oxygen species (ROS); generation of advanced glycation end-products (AGEs); activation of the polyol pathway; and decreased glycosaminoglycan content in basement membranes (Fig. 2). Mechanical stretch is also involved in the pathogenesis of DN. Increased intraglomerular pressure (hyperfiltration), causing stretch of the mesangial cells, produces an up-regulation of glucose transporter-1 (GLUT-1) that ultimately leads to over-expression of TGF-β1 and ECM production, resulting in glomerulosclerosis (Fig. 3).[2] It must be noted that high levels of glucose have also been shown to up-regulate GLUT-1 in the mesangial cells.[2] Several studies have shown that the kidneys can be protected in diabetes by manipulating the various cellular pathways activated by hyperglycaemia. Few other renal diseases follow the predictable and well-characterised evolutionary process of DN (Table II).

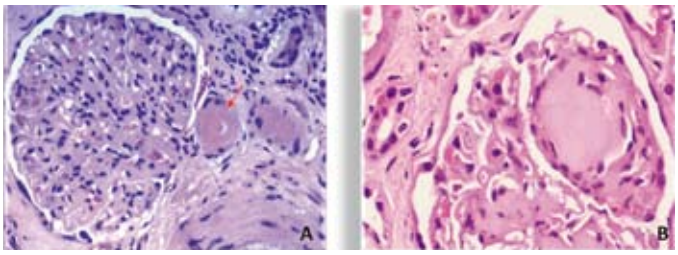


*Fig. 1. Light microscopic features of diabetic nephropathy. Light microscopic images (haematoxylin and eosin) in diabetic patients. (A): Diffuse thickening of the basement membrane of the capillary loops, increase of mesangial matrix and hyaline thickening of the arteriole (red arrow). (B): Nodular sclerosis of the glomerulus (Kimmelstiel-Wilson nodules).*

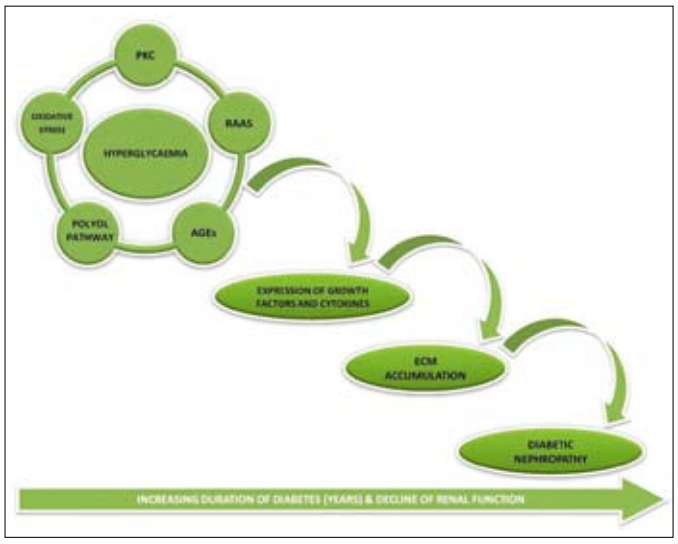


*Fig. 2. Cellular pathways of diabetic nephropathy. (PKC – protein kinase C, RAAS – renin-angiotensin-aldosterone system, AGEs – advanced glycation end-products, ECM – extracellular matrix.)*

## 'Traditional' renoprotective measures

There is sufficient evidence that certain therapies protect the kidneys from the long-term effects of DM. These so-called 'traditional' reno-protective measures form the basis of current prevention and treatment approaches to DN (Table III).

### Blood pressure control

Arterial hypertension is a major risk factor for the progression of DN and treatment of hypertension to lower blood pressure (BP) targets in diabetics (130/80 mmHg) leads to cardiovascular and microvascular

**Table II. Stages of diabetic nephropathy**

| Stage | GFR | Albuminuria | Blood pressure | Time course from diagnosis (yrs) |
|---|---|---|---|---|
| Glomerular hyperfiltration | Elevated (25 - 50%) | Absent | Normal | At diagnosis |
| Clinical latency | High normal | Absent | Normal | Variable (0 - 5) |
| Incipient nephropathy (microalbuminuria) | Normal (may be slightly reduced) | 20 - 200 µg/min (30 - 300 mg/day) | Normal to slightly elevated | 5 - 15 |
| Overt nephropathy (macroalbuminuria) | Reduced | >200 µg/min (>300 mg/day) | Elevated | 10 - 15 |
| ESRF | Reduced | Massive | Elevated | 15 - 30 |

GFR – glomerular filtration rate; ESRF – end-stage renal failure.

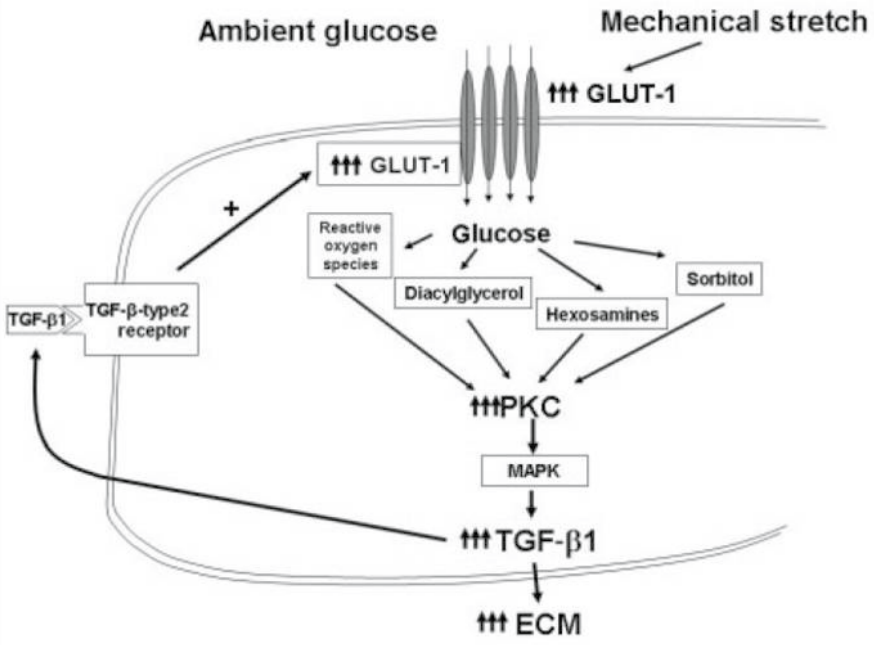


*Fig. 3. Cellular pathways mediating mechanical stretch-induced GLUT-1 upregulation in mesangial cells. (GLUT-1 – glucose transporter-1, TGF-β1 – transforming growth factor β1, PKC – potein kinase C, ECM – extracellular matrix, MAPK – mitogen activated protein kinase (Gnudi and Viberti, 2007[2] – permission from Oxford Journals).)*

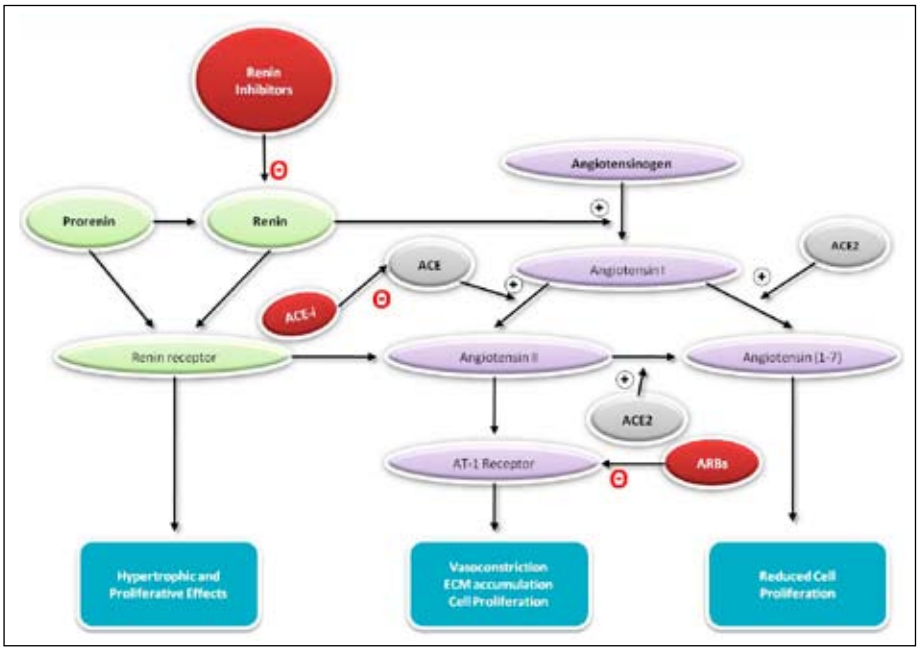


*Fig. 4. The RAAS pathway. (ACE – angiotensin-converting enzyme, ACE-I – ACE inhibitor, ARB – angiotensin-receptor blocker, AT-1 – angiotensin-1 receptor, RAAS – renin-angiotensin-aldosterone system, ⊕ – stimulation, Θ – inhibition.)*

**Table III. Renoprotective measures in diabetes mellitus**

**Traditional measures**

- Blood pressure control
- Blockade of the renin-angiotensin-aldosterone system (RAAS)
- Glycaemic control
- Lipid reduction
- Smoking cessation
- Weight reduction

**Novel and experimental renoprotective measures**

- Direct renin inhibitors (aliskiren)
- Glycosaminoglycans (sulodexide)
- Inhibitors of PKC (ruboxistaurin)
- Inhibitors of AGEs (piridoxamine)
- Antifibrotic agents (TGF-β inhibitors, PAI-1 inhibitors, pirfenidone)

risk reduction. In the United Kingdom Prospective Diabetes Study (UKPDS) there was a 29% reduction in the risk of development of microalbuminuria by a 10 mmHg reduction in systolic BP (SBP), and the smallest risk of microvascular complications was seen in patients with SBP <120 mmHg.[3] Although the use of agents that block the renin-angiotensin-aldosterone system (RAAS) pathway lowers BP and is currently central to renoprotection in DN, the use of other agents to control BP is equally important.

## RAAS blockade

RAAS is a major pathway (Fig. 4) involved in progressive renal disease. Angiotensin II, the main effector of this pathway and a potent vasoconstrictor, causes glomerular hyperfiltration, mesangial cell proliferation, ROS generation and expansion of ECM, leading to tissue fibrosis. Several studies have investigated the role of agents that block RAAS in preventing and/or retarding the progression of nephropathy in patients with type 1 DM (T1DM) and type 2 DM (T2DM). In the Heart Outcomes Prevention Evaluation (HOPE) study,[4] treatment with ramipril was associated with a reduced incidence of macroalbuminuria in patients with diabetes and a 22% lowering in the incidence of myocardial infarction, stroke or death from a cardiovascular cause compared with placebo. In the Irbesartan Diabetic

Nephropathy Trial (IDNT) doubling of serum creatinine, development of ESRD, or death from any cause, was reduced by 20% with irbesartan compared with placebo ($p$=0.02), and by 23% with irbesartan compared with amlodipine ($p$=0.006).[5] The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study in which patients with T2DM and nephropathy were randomised to losartan or placebo in addition to conventional treatment reported a 16% risk reduction ($p$=0.02) of primary outcome in patients treated with losartan compared with the placebo group.[6] These studies and many others show that the use of agents that block RAAS is effective in the prevention of DN.

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### Glycaemic control

There are numerous studies to show that the DN risk is higher in patients with poor metabolic control. The Diabetes Control and Complications Trial (DCCT) and UKPDS have demonstrated the importance of intensive glycaemic control in reducing the risk of the development of microalbuminuria. In the DCCT, intensive glycaemic control (close to the normal range) in T1DM patients reduced the occurrence of microalbuminuria by 39% (95% CI: 21 - 52%) and albuminuria by 54% (95% CI: 19 - 74%), thus concluding that intensive therapy effectively delays the onset and slows the progression of DN in patients with T1DM.[7] The UKPDS compared the effects of intensive glycaemic control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with T2DM.[8] Over 10 years, haemoglobin $A_{1c}$ ($HbA_{1c}$) was 11% lower in the intensive group compared with the conventional group and there was a 25% reduction (7 - 40; $p$=0.0099) in microvascular endpoints. Therefore, intensive glycaemic control by either sulphonylureas or insulin was shown to significantly reduce the risk of microvascular complications.

### Lipid reduction

Lipids may have a direct role in the pathogenesis of chronic kidney disease (CKD) and may contribute to the high risk of cardiovascular morbidity and mortality associated with DN. The mechanisms of renal injury by hyperlipidaemia include the inhibition of lipoprotein lipase activity in vascular endothelial cells, and the attenuation of renal injury induced by AGEs in the absence of hyperlipidaemia.[9] A meta-analysis of 12 studies that examined the effects of lipid-lowering drugs on diabetic renal disease showed that interventions to lower lipid levels preserve the glomerular filtration rate, regardless of diabetes status.[10]

### Smoking cessation and weight reduction

Smoking is a recognised risk factor for DN and contributes to its progression. Cessation of smoking is therefore strongly recommended after the diagnosis of DN. There is ample evidence that obesity independently contributes to the development and progression of CKD. In obese individuals, glomerular hyperfiltration due to the increased metabolic needs of obesity is postulated to lead to the development of glomerulosclerosis through a similar mechanism to that in DN. Although the impact of weight loss on proteinuria and renal function is unclear, a recent meta-analysis has shown that for each 1 kg weight loss, there was a significant reduction in proteinuria ($p$<0.001) and microalbuminuria ($p$=0.011).[11]

## Novel and experimental reno-protective measures

As current traditional therapies, especially RAAS blockade, have consistently shown success in slowing the progression of DN, newer therapies to treat this condition are also coming to light and some are discussed below.

### Aliskiren

Aliskiren is an oral renin inhibitor, highly specific for renin, and therefore able to lower the level of angiotensin I and II and that of aldosterone. It significantly reduces the expression of TGF-β, which together with angiotensin II has a significant role in the progression of renal fibrosis in DN. Renin inhibition with aliskiren causes a more complete blockade of RAAS and reduces the feedback effects when compared with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs). Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial assessed the renoprotective effects of dual blockade of RAAS by adding treatment with aliskiren. Daily treatment with 300 mg aliskiren, compared with placebo, reduced the mean urinary albumin-creatinine ratio (ACR) by 20% (95% CI: 9 - 30%; $p$<0.001), with a reduction of 50% or more in 24.7% of patients who received aliskiren compared with 12.5% of those who received placebo ($p$<0.001).[12] A much larger and longer trial of aliskiren with hard clinical endpoints (ALTITUDE) is currently ongoing and is designed to evaluate the benefits of adding aliskiren to conventional treatment, including either an ACE inhibitor or an ARB.

### Sulodexide

Sulodexide is a purified mixture of glycosaminoglycans with a renoprotective mechanism of action thought to be related to: (*i*) restoration of glomerular glycoproteins present in the glomerular basement membrane (GBM) and mesangium; (*ii*) restoration of the anionic heparin sulphate charge on the GBM; and (*iii*) suppression of high glucose-induced overexpression of TGF-β, responsible for enhanced expression of mesangial matrix and collagens. A study of 149 patients with T2DM and microalbuminuria, randomised to 200 mg and 400 mg of sulodexide compared with placebo, reported attainment of a primary endpoint (50% reduction in ACR or return to normoalbuminuria) in 33.3%, 18.4% and 15.4%, respectively.[13] In the Diabetic Nephropathy Albuminuria Sulodexide (DiNAS) study, patients with T1DM and T2DM with albuminuria were randomised to sulodexide 50 mg, 100 mg and 200 mg daily and placebo for 4 months. Albuminuria was reported to have decreased by 30%, 49% and 74%, respectively, compared with the placebo group.[14] However, in a much larger study of 1 000 patients with DM and persistent microalbuminuria, the sulodexide microalbuminuria trial (SUN-Micro-Trial), there was failure to achieve the primary endpoint of reduction in urine albumin excretion.[15]

### Ruboxistaurin (RTX)

Overexpression of PKC is important in the pathogenesis of DN. Activated PKC causes renal injury by enabling oxidative stress and by the activation of TGF-β to induce ECM production by the mesangial cells.[2] RTX inhibits PKC-β and in animal studies has been shown to reduce the production of ECM protein and TGF-β1, thereby reducing albuminuria. In a study of 123 patients with DN randomised to receive either 32 mg of RTX or placebo daily for 1 year, patients treated with RTX experienced a 24% reduction in albuminuria compared with those treated with placebo.[16] Also, renal function (eGFR) remained stable in the RTX group but was reported to have declined in the placebo group.

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### Pyridoxamine

Pyridoxamine is an active inhibitor of AGEs. Its mode of action is also not clear but is probably through: (*i*) inhibition of the breakdown of amadori products (an intermediate in the production of AGEs as a result of glycation); (*ii*) reducing the toxic effects of ROS; and (*iii*) scavenging of reactive carbonyl compounds. In a phase 2 trial of 84 patients with DN, randomised to receive either pyridoxamine 250 mg or placebo in addition to standard therapy for DN, there

was a 48% reduction of baseline serum creatinine as well as a decreased urinary excretion of TGF-β compared with baseline in the pyridoxamine group in comparison with the placebo group. There was however no change in urinary albumin excretion (uAE) in either group from baseline.[17]

### Antifibrotic agents

TGF-β plays a key role in the process of progressive renal fibrosis, being involved in the accumulation of ECM. Therapies that target TGF-β and prevent progression of renal fibrosis have the potential to retard, or even reverse, many of the long-term alterations associated with DN. Some of the downstream effects of TGF-β are regulated through plasminogen activator inhibitor (PAI-1) and connective tissue growth factor (CTGF). *In vivo* and *in vitro* studies are being conducted to test the antifibrotic properties of anti-TGF-β antibodies and anti-CTGF antibodies. Of interest, there are now also inhibitors of PAI-1. Pirfenidone, a direct inhibitor of TGF-β, holds some promise.

## Conclusion

Simple measures such as adequate BP control, intensive glycaemic control, smoking cessation and use of RAAS blockade can positively retard the progression of DN. Results of some large randomised controlled studies of newer agents may open new doors for the prevention and treatment of DN.

**References available at www.cmej.org.za**

## In a nutshell

- There is a global increase in the incidence of end-stage renal disease in patients with diabetes mellitus.
- Large organisations are putting in place programmes that emphasise the importance of early detection of diabetic kidney disease.
- Hyperglycaemia plays a central role in the pathogenesis of diabetic nephropathy.
- Some of the key pathways involved in diabetic nephropathy include the polyol pathway, activation of protein kinase C, generation of advanced glycation products, activation of cytokines and generation of reactive oxygen species.
- Kimmelstiel-Wilson nodules are the histological hallmark of diabetic nephropathy, other features being hyalinosis of the arterioles.
- Traditional renoprotective measures, such as RAAS inhibition, weight loss, smoking cessation, blood pressure control and glycaemic control, still play a central role in protecting the kidneys from the injurious effects of diabetes.
- Some novel approaches to renoprotection include the use of antifibrotic agents, restoration of the glycosaminoglycan content of the basement membranes, inhibition of protein kinase C and inhibitors of advanced glycation end-products formation.
- Although RAAS blockade is very important in renoprotection, blood pressure control using other types of antihypertensive drugs is still very useful.
- Results of the ALTITUDE trial are awaited and expected to shed light on the use of a new RAAS inhibitor (aliskiren – a direct renin inhibitor) in the prevention of nephropathy in diabetics.
- Most of the newer therapies are still in the experimental phase of development.