Recent advances in diabetic nephropathy

Sally M Marshall

ABSTRACT – Diabetic nephropathy is the most common cause world-wide of renal failure requiring renal replacement therapy, most patients having type 2 rather than type 1 diabetes. Cardiovascular risk increases progressively as nephropathy develops. In addition to abnormalities in the glomerular endothelium and mesangium, recent data suggest that changes are also seen in the glomerular epithelial cell or podocyte. The foot processes of the podocyte broaden and efface and there is loss of podocyte specific proteins such as nephrin. Eventually there is loss of podocytes themselves. These changes may contribute to proteinuria.

The development of nephropathy can be prevented by good glucose and blood pressure control. Once microalbuminuria or proteinuria are present, control of intraglomerular pressure, using inhibitors of the renin-angiotensin system, and control of systemic blood pressure are paramount, and can delay the need for renal replacement therapy by many years. Aggressive management of cardiovascular risk factors also slows the progression of nephropathy and prevents cardiovascular events.

KEYWORDS: cardiovascular risk, diabetic nephropathy, glomerulosclerosis, intraglomerular hypertension, mesangial expansion, microalbuminuria, podocyte

Diabetic nephropathy develops over many years in a subset of people with diabetes. Increasing urine albumin excretion is accompanied by rising blood pressure and cardiovascular risk. At a relatively late stage, glomerular filtration begins to fall and eventually end-stage renal disease (ESRD) is reached. This will not be a comprehensive review of diabetic nephropathy. Instead, it will focus on three main areas: natural history, pathophysiology and management, concentrating on recently published data and on previously neglected or controversial areas.

Natural history of diabetic nephropathy

Current prevalence of end-stage renal disease in diabetes

It is difficult to obtain precise data on the incidence of end-stage renal disease (ESRD) due to diabetes worldwide for a number of reasons: not every country has a renal register; even in those countries with a register, data are often incomplete; methods of reporting differ between registries; data are on those individuals accepted on to renal replacement therapy (RRT) so are inevitably an underestimate. However, despite these caveats, recent data from many countries show that diabetes is the commonest single cause of ESRD. In the USA, the number of individuals with diabetes entering RRT programmes is now around 140 per million population.[1] In Europe, the incidence is lower, ranging from 42.5 per million population in Austria to 15.1 in the Netherlands.[2] Data from the UK Renal Registry are incomplete, but the UK incidence appears to be towards the lower end of the European range.[3] In almost all countries, the numbers of people with diabetes entering RRT programmes has increased steadily over the last 10 years.[1] However, in the USA incidence rates appear to be levelling off, and in the UK the rise has been much less marked than in other countries.

In addition to wide variation between countries in the absolute incidence of new cases requiring RRT due to diabetes, the proportion of cases due to diabetes also varies enormously.[1] The countries with the highest proportion due to diabetes are Brunei and USA (~45% of the total population), with the lowest figures in Russia (<5%). At least some of this difference between countries relates to the different prevalence of diabetes, particularly type 2 diabetes.

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Key Points

- **Diabetic nephropathy is now the most common cause world-wide of renal failure requiring renal replacement therapy, the majority of patients having type 2 rather than type 1 diabetes**
- **The natural history of nephropathy in Caucasian type 2 diabetes is similar to that in type 1, whereas in non-Caucasian individuals, nephropathy is more common and progresses faster**
- **Cardiovascular risk is increased at all stages of nephropathy and rises acutely as nephropathy progresses**
- **Diabetic nephropathy can be prevented by tight blood glucose and blood pressure control**
- **Multifactorial intervention with intensive life-style and aggressive management of blood pressure, blood glucose and blood lipids, significantly reduces the rate of progression of diabetic nephropathy and its associated cardiovascular disease**

In many countries now, the majority of people with diabetes entering RRT have type 2 not type 1 diabetes. In the USA, 71% have type 2 diabetes[1] whilst in UK the figure is around 31%.[3] The proportion of individuals entering RTT with type 2 diabetes is higher in those from indigenous populations and from the ethnic minorities; for example in the USA, 63% of Europid patients have type 2 diabetes, whilst 81% of Native American and 75% of Afro-American individuals have type 2 diabetes.[3] Similarly, in Australia, 48% of Europid diabetic patients beginning RRT have type 2 diabetes, whilst in the Aboriginal RRT diabetic population, 85% have type 2 diabetes.

Is the natural history of diabetic nephropathy in type 1 diabetes changing?

The above data would suggest that the incidence of ESRD due to diabetes is increasing, but is this true? Classical work reported in the 1980s suggests that after 25–30 years duration of diabetes, the cumulative incidence of proteinuria in both type 1 and type 2 diabetes is approximately 30%.[4,5] In type 1 diabetes, the peak annual incidence of developing proteinuria was 4–5% at 15–20 years duration and then the incidence declined sharply, although there was a small further peak in incidence around 30–35 years duration.[6] In the initial studies of earlier stages of nephropathy, approximately 50% of individuals with type 1 diabetes developed microalbuminuria.[7,8]

However, recent studies reporting in the 1990s suggest that the incidence of microalbuminuria has fallen to around 35–40% and of proteinuria to 15–20%.[9–12] This has been interpreted as prevention of nephropathy because of improved management, primarily of blood pressure. However, another interpretation might be simply that the appearance of microalbuminuria or proteinuria has been delayed. On the basis of data from one study in a small number of type 1 diabetic patients with microalbuminuria, it was suggested that in patients with long duration (>15 years) diabetes, microalbuminuria was of lesser significance than in short-duration patients.[13] Long-duration individuals were thought to be at much less risk of progression to proteinuria and ESRD than shorter-duration individuals. Two recent studies challenge this interpretation.[14,15] In one of them, individuals with type 1 diabetes for >30 years were followed for seven years.[14] Of the 87 patients who were normoalbuminuric at baseline, 24% developed persistent microalbuminuria and 4% persistent proteinuria. Of the 19 initially microalbuminuric patients, 32% developed proteinuria. In addition, the seven-year survival was significantly less in those with microalbuminuria at baseline compared to the normoalbuminuric patients (50 *vs* 85%). Thus it would seem that even in long duration diabetes, microalbuminuria remains a significant risk factor for premature death and for the development of proteinuria. In addition, these data might suggest that the natural history of nephropathy may be changing. Rather than preventing the development of nephropathy, improvements in care may be delaying it. This has important implications for screening programmes for nephropathy and for the management of patients with long-duration diabetes.

Thus, over a lifetime of diabetes, about 50% of individuals will develop microalbuminuria, at a rate of 2–4% per annum (Fig 1). Of those with microalbuminuria, 20–30% develop proteinuria in 10–20 years and eventually ESRD. A further 40% will remain microalbuminuric, and perhaps will eventually progress to proteinuria. The remaining 20–30% will revert to normal albumin excretion, even after several years of microalbuminuria.[16] The reasons for these differences in behaviour are not clear but are likely to centre around control of blood pressure and perhaps blood glucose. Thus the overall natural history of nephropathy in type1 diabetes has changed. Onset is probably later and progression slower than previously thought. It is no longer safe to assume that because an individual has not developed proteinuria after 30 years duration diabetes, they will not do so.

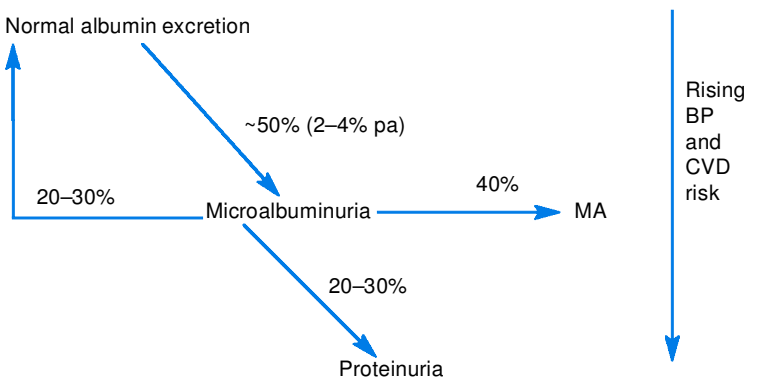

Fig 1. Natural history of the development of diabetic nephropathy in type 1 diabetes.

The natural history of diabetic nephropathy in type 2 diabetes

In type 2 diabetes, at least in Europid populations, the natural history of nephropathy is remarkably similar to that in type 1 diabetes. The UK Prospective Diabetes Study (UKPDS) has recently reported transition rates of 2% per annum from normoalbuminuria to microalbuminuria, 2.8% per annum from microalbuminuria to proteinuria and 2.3 % per annum from proteinuria towards ESRD.[17] These figures are very close to those reported for type 1 diabetes. The UKPDS has also confirmed the increasing risk of premature mortality, generally from cardiovascular disease, with increasing evidence of nephropathy. Annual death rates in the UKPDS were 0.7, 2.0, 3.5 and 12.1% for people with normal albumin excretion, microalbuminuria, proteinuria and elevated serum creatinine, respectively.

In non-Caucasian populations, rates of development of microalbuminuria and proteinuria are probably higher than in Caucasian individuals and the rate of progression of nephropathy may be faster. The most intensively studied population is the Pima Indians, where longitudinal studies have been performed. The rate of progression from normal albumin excretion to

Box 1. Metabolic and clinical characteristics of diabetic patients with albuminuria and their first degree relatives.

Insulin resistance
High triglycerides
Low HDL-cholesterol
Hypertension
Cardiovascular disease
Premature cardiovascular mortality

HDL = high-density lipoprotein.

microalbuminuria is at least 4% per annum and more than 50% develop proteinuria within 20 years duration diabetes.[18,19] In contrast to the apparent decline in cumulative incidence of proteinuria in European type 1 diabetic patients, in the Pima Indians the incidence has doubled in the last 40 years, despite improvements in glucose and blood pressure control.[20]

Pathophysiology of diabetic nephropathy

Genetics

The observation that only a subset of people with diabetes develop nephropathy has led to the belief that there is a genetic susceptibility to nephropathy. In addition to renal disease and premature cardiovascular mortality, people with diabetic nephropathy have a number of other metabolic and pathophysiological abnormalities, listed in Box 1. Many of these abnormalities are also seen in first degree relatives of diabetic nephropathic patients, who also have a higher prevalence of hypertension and cardiovascular disease than first degree relatives of people with diabetes without nephropathy.[21,22] Thus any genetic susceptibility must link premature cardiovascular and renal disease. A number of candidate genes have been suggested but there is no convincing evidence of a major effect of any gene tested so far.

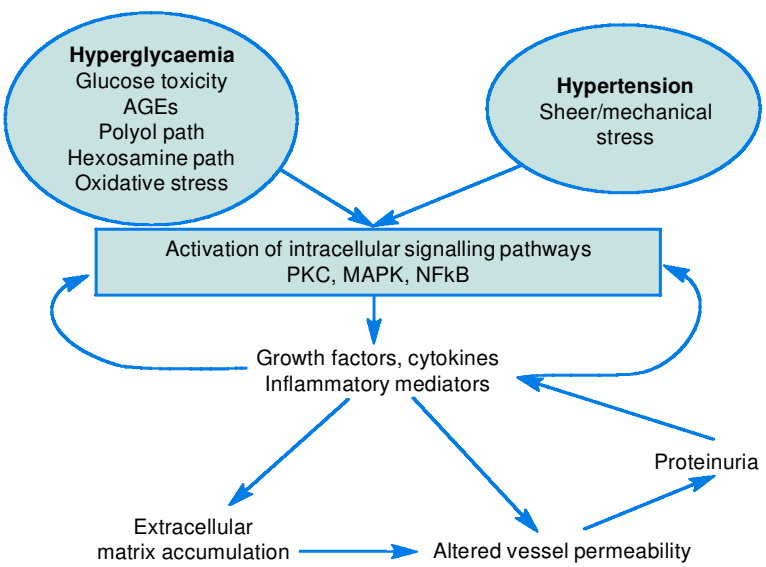

Fig 2. Biochemical factors important in the development of diabetic nephropathy.

Biochemical mechanisms

Hyperglycaemia and glomerular hypertension are the two main initiating and progression factors thus far identified in the development of nephropathy. Hyperglycaemia probably acts via direct glucose toxicity, glycation and increased flux through the polyol and hexosamine pathways (Fig 2). Recently, it has been suggested that hyperglycaemia-induced overproduction of superoxide by the mitochondrial electron transport chain may be the fundamental abnormality stimulating these individual pathways.[23]

Proteinuria

In the glomerulus in diabetes, protein passes across the endothelial cells of the glomerular capillaries, across the basement membrane and through the slit pores of the glomerular epithelial cells (podocytes) into Bowman's space (Fig 3). Previously, work has focused on changes within the glomerular vasculature and its supporting basement membrane and mesangium. Because of relative constriction of the efferent glomerular arteriole compared to the afferent arteriole, transglomerular pressure is increased in diabetes and contributes to proteinuria and possibly the development of glomerulosclerosis. Changes in the basement membrane are also well described. On electron microscopy, the basement membrane is thickened. Biochemically, there is loss of negatively charged glycosaminoglycans from the basement membrane, particularly of heparan sulphate, allowing increased passage of anionic albumin and thus a relatively selective proteinuria. Later, clearance studies of neutral dextrans suggest the development of large pores in the basement membrane, leading to non-selective proteinuria, with loss of large molecules.

Changes occurring in the mesangium are also well documented. Microscopically, there is mesangial matrix expansion, either generally or in a nodular pattern (the classical Kimmelsteil-Wilson kidney). An increase in mesangial cell number also occurs. As disease advances, there is a close relationship between mesangial expansion and declining glomerular filtration. Mesangial expansion also correlates inversely with capillary-filtration surface area, which itself correlates to glomerular filtration rate (GFR).

Recently attention has focused on the glomerular epithelial cell or podocyte. The podocyte has a cell body with numerous foot processes which rest on the outer surface of the basement membrane, probably providing support for the glomerulus (Fig 3). The foot processes interdigitate, so that adjacent foot processes always arise from different podocyte cell bodies. The surface of the podocyte, like the basement membrane, is covered in negatively charged molecules, including podocalyxin (Fig 4). The podocyte also has an active cytoskeleton to which transmembrane molecules such

as podocalyxin are attached via adaptor molecules. The spaces between the podocyte foot processes are called the slit spaces. These contain the protein nephrin, amongst others. Molecules of nephrin are thought to form a zip-like structure across the slit space, which controls the passage of protein into Bowman's space.

In both human and experimental diabetes, podocyte morphology is abnormal. The foot processes broaden and efface. Eventually there is loss of the podocyte itself.[24] Podocytes cannot regenerate so this loss cannot be compensated for. There is also decreased expression of nephrin mRNA and protein.[25] Abnormalities in several podocyte proteins have been demonstrated to cause proteinuric renal diseases in humans, for example: absence of nephrin in Finnish congenital nephritic syndrome; CD2-adaptor protein and podocin in forms of steroid-resistant nephritic syndrome. Thus it is possible that podocyte protein abnormalities in diabetes contribute to proteinuria and eventual glomerulosclerosis.

Recent advances in the management of diabetic nephropathy

Blood glucose control

In the prevention of diabetic nephropathy, good control of blood glucose is essential. Both the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes demonstrated that the lower the HbA_{1c} the lower the risk of developing nephropathy. There was no HbA_{1c} level below which benefit was not gained, ie no threshold. Thus, suggested targets for HbA_{1c} are <7.0%, provided this can be achieved without unacceptable hypoglycaemia.

Once microalbuminuria or proteinuria is present, there is little evidence that improving glucose control delays progression of nephropathy. Trials that have been performed have been too small, of insufficient length or have failed to reach adequate glucose control. However, good glucose control obviously remains essential for other aspects of diabetes care.

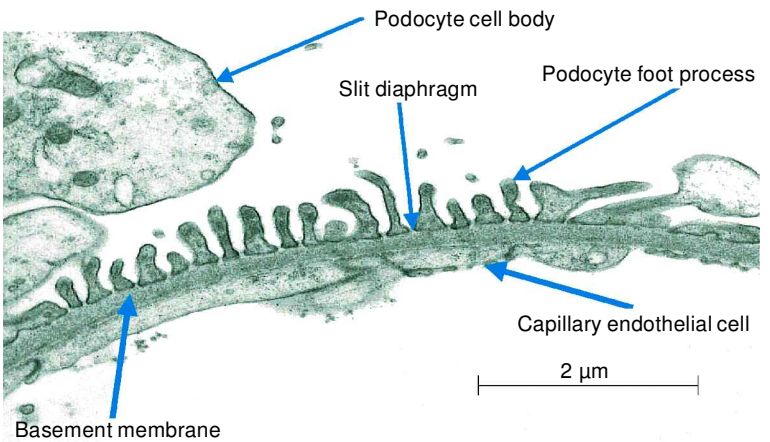

Fig 3. Electron micrograph of the components of the glomerular filtration barrier.

Control of intraglomerular pressure and systemic blood pressure

Perhaps the most important development in the management of diabetic nephropathy in the last 10 years has been the demonstration of the importance of adequate control of systemic blood pressure and intraglomerular pressure, particularly using inhibitors of the renin-angiotensin system (RAS).

The blood pressure arm of the UKPDS demonstrated that tight blood pressure control reduced the risk of developing nephropathy in type 2 diabetes. A maximum acceptable blood pressure for someone with type 2 diabetes and normal albumin excretion is considered to be 140/80 mmHg, levels above this requiring treatment with the most appropriate class of antihypertensive agent for the individual patient. In type 1 diabetes, there have been no good trials of the effect of antihypertensive therapy in preventing nephropathy in normoalbuminuric individuals.

Once microalbuminuria or proteinuria is present, there is much evidence that control of intraglomerular pressure, particularly using inhibitors of the RAS, and control of systemic blood pressure can greatly slow the progression to end-stage renal failure.

A recent meta-analysis of papers examining the effect of angiotensin-converting enzyme (ACE) inhibition compared to placebo in microalbuminuric type 1 diabetic patients confirmed that ACE inhibition reduces the risk of developing proteinuria by 60% and increased the likelihood of reverting to normal albumin excretion three-fold over two years.[26] Interestingly, the beneficial effects of ACE inhibition in reducing albumin excretion appeared to wane with time, being significantly less after four years treatment compared to one year, lending support to the concept of delay rather than prevention of proteinuria. In most of these studies, systemic blood pressure was <130/80 mmHg at entry and around 120/70 mmHg during treatment. This has led to the suggestion that young type 1 diabetic patients with microalbuminuria or proteinuria should be prescribed ACE inhibitors regardless of their blood pressure. At the proteinuric stage, there is also good evidence that very tight blood pressure control, using ACE inhibitors with the addition of other agents as necessary, significantly delays progression. Target blood pressure levels for type 1 patients with microalbuminuria are 120/70 mmHg and for proteinuria <130/75 mmHg. Patients should be prescribed ACE inhibitors to the maximum tolerated dose initially, with other agents being added as necessary.

In type 2 diabetes, the largest trials have been performed using angiotensin II receptor antagonists rather than ACE inhibitors. Three large studies examined the effects of angiotensin II receptor antagonists (ATIIRBs) in type 2 diabetic patients with microalbuminuria[27] or advanced nephropathy.[28,29] In microalbuminuria, treatment with irbesartan reduces the risk of progression to proteinuria by 40 % compared to placebo.[27] In more advanced nephropathy, the risk of progression of nephropathy was reduced 20–25% compared to placebo[28,29] or amlodipine.[29] However,

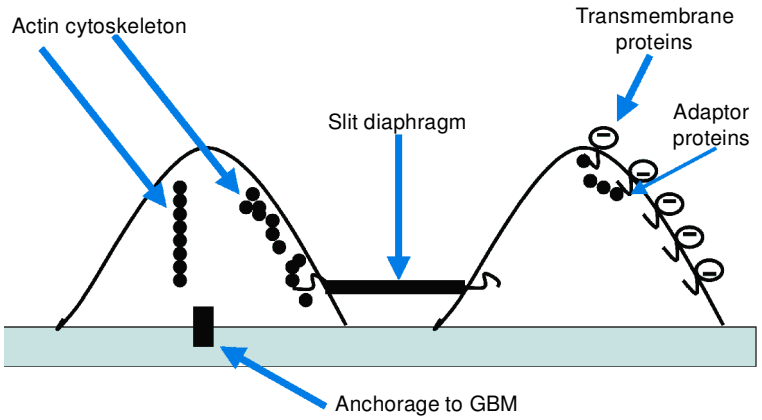

Fig 4. Diagram illustrating the component parts of the foot process of the glomerular epithelial cell (the podocyte).

none of these studies showed any cardiovascular benefit. Thus, as with type 1 diabetes, type 2 diabetic patients with microalbuminuria or proteinuria should be offered therapy with an RAS inhibitor in the maximum tolerated dose initially, with other classes of agent being added as necessary to achieve a target blood pressure <135/75 mmHg.

Several relatively small, short-term studies in both type 1 and 2 diabetes have demonstrated similar reductions in blood pressure and albumin excretion with ACE inhibitors and ATIIRBs. Addition of the two classes of drug further reduces blood pressure and proteinuria. Longer-term studies demonstrating harder end-points and the safety of combination therapy are awaited.

Reduction in protein intake

Fears of malnutrition and the practical difficulties in achieving low protein intake have limited recommendations on protein intake. However, the consensus view is that diabetic patients should be encouraged not to eat excessive amounts of protein but not to restrict intake below 1.0–1.2 g/kg body weight per day.

Managing cardiovascular risk in diabetic nephropathy

As discussed above, cardiovascular risk increases dramatically as nephropathy progresses. Aggressive management of cardiovascular risk factors is thus extremely important and is likely to be doubly beneficial: progression of nephropathy is likely to be slowed as well as cardiovascular risk reduced. One study has reported on a multifactorial intervention in microalbuminuric type 2 diabetic patients.[30] Patients were randomised to usual care or to an intensive lifestyle and medical intervention regimen according to a target-driven protocol. In the intensive group, extra effort was made to encourage weight loss, increased exercise and smoking cessation and stricter targets for HbA_{1c}, lipids and blood pressure set. Aspirin, statins and ACE inhibitors were prescribed for everyone in the intensive group. Over an eight-year follow-up, in the intensively treated group, cardiovascular morbidity and mortality was decreased by 50%, progression to proteinuria by 60% and retinopathy by 60%. Thus, all diabetic patients with nephropathy will almost certainly gain renal and cardiovascular benefit from aggressive attack of cardiovascular risk factors.

Thus, there is convincing evidence that effective implementation of current treatment modalities can greatly improve the outlook for diabetic patients with early nephropathy. The challenge remains to ensure that everyone with diabetes has access to such treatment. Audit studies from the UK have demonstrated that when first seen in specialist renal clinics, the majority of patients with diabetes are under-treated, not receiving inhibitors of RAS, statins or aspirin and in poor glucose control.[31]

Conclusions

Despite general improvements in diabetes care, the number of individuals with end-stage renal disease continues to increase, so that worldwide, diabetes is now the single commonest cause of entry to RRT programmes. Good clinical management, particularly tight control of hypertension and other cardiovascular risk factors, improves both the renal and cardiovascular outcome. With the current explosive increase in the incidence of diabetes, particularly type 2 diabetes, we risk an epidemic of ESRD due to diabetes, unless proven clinical interventions are offered to everyone with diabetes.

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