

Recent advances in diabetic nephropathy

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Diabetic nephropathy is the leading cause of end stage renal disease worldwide and is associated with increased cardiovascular risk. The earliest clinical manifestation is of microalbuminuria. Tight blood glucose and blood pressure control reduce the risk of microalbuminuria. Once microalbuminuria is present, the rate of progression to end stage renal disease and of cardiovascular disease can be delayed by aggressive management of blood pressure, glucose, and lipids. Inhibition of the renin-angiotensin system is important to reduce intraglomerular pressure but other classes of antihypertensive agent may also be needed to gain adequate control of systemic blood pressure. Such measures can at least half the rate of progression of nephropathy and cardiovascular disease.

glomerular filtration over a further 10 years, until end stage renal failure is reached.

In type 1 diabetes, the older literature suggests that the cumulative incidence of microalbuminuria after 30 years of diabetes is approximately 50% and that 30%–40% of patients will develop proteinuria.¹ The incidence of proteinuria peaked at 4%–5% around 15–20 years' duration, with a smaller peak at 30–35 years' duration.² More recent work, however, suggests that the appearance of nephropathy may be being delayed.^{3–7} The cumulative incidence of microalbuminuria and proteinuria in several more recent studies is 35%–40% and 25% respectively after 25–30 years of diabetes (fig 1). Initial, older studies suggested that 80% of type 1 diabetic patients with microalbuminuria would progress to proteinuria.^{8–9} However, more recent studies suggest that around one third of microalbuminuric patients will revert to normal albumin excretion and only one third progress to proteinuria.^{10–12} In addition, in one small study, 24.4% of initially normoalbuminuric type 1 diabetic patients with duration of diabetes >30 years developed microalbuminuria or proteinuria in a seven year follow up.¹³ Also in this study, 32% of the initially microalbuminuric patients progressed to proteinuria, in contrast to earlier suggestions that microalbuminuria in long duration diabetes was a benign condition.¹⁴

Thus, the classical natural history of the development of nephropathy in type 1 diabetes is undoubtedly being modified (box 2). Microalbuminuria develops at around 2%–3% a year, with a cumulative incidence over a lifetime of diabetes of approximately 50%. Around one third of individuals with microalbuminuria will progress to proteinuria, at a rate of 2%–3% a year, and almost all proteinuric patients eventually develop end stage disease. One small study has suggested that microalbuminuria and proteinuria may appear at any duration of diabetes, long duration patients not being protected.

The classical definition of diabetic nephropathy is of a progressive rise in urine albumin excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually end stage renal failure. Patients generally have diabetic retinopathy. Recently, greater appreciation of the close links between nephropathy and cardiovascular disease have led to the inclusion of premature cardiovascular disease, cardiovascular risk increasing in parallel with albuminuria (box 1). Diabetic nephropathy is now the single commonest cause of end stage renal failure worldwide and is acknowledged as an independent risk factor for cardiovascular disease. In many countries, the majority of diabetic patients starting renal replacement therapy now have type 2 rather than type 1 diabetes. This review will therefore encompass nephropathy in both type 1 and type 2 diabetes.

NATURAL HISTORY OF NEPHROPATHY

Type 1 diabetes

The initial rise in protein excretion is small and highly selective, albumin being the main protein excreted in excess. At this stage, specific immunologically based assays detect small increases in urine albumin which are below the detection limit of conventional dipstick tests (table 1). This so-called microalbuminuria generally appears within 5–15 years' duration of diabetes. Without specific intervention, over approximately a further 10 years, albumin excretion slowly increases through the microalbuminuric range, until dipstick positive or conventional proteinuria is present. Glomerular filtration generally does not begin to fall until proteinuria is present, when, untreated, there is a progressive decline in

Type 2 diabetes

In white individuals, the development of diabetic nephropathy follows a similar course to that in type 1 diabetes. The cumulative incidence of proteinuria in white type 2 diabetic patients is similar to that of type 1 patients. Several studies have demonstrated rates of development of microalbuminuria and proteinuria in type 2 diabetic patients that are approximately comparable to those in type 1 patients.^{15–16}

Abbreviations: ACE, angiotensin converting enzyme; ATIIRB, angiotensin II receptor antagonist; DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; RRT, renal replacement therapy; UKPDS, United Kingdom Prospective Diabetes Study

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Table 1 Definitions used in diabetic nephropathy

	Normal	Microalbuminuria	Proteinuria
Albumin:creatinine ratio (mg/mmol)			
Men	<2.5	2.5–30	>30
Women	<3.5	3.5–30	>30
Albumin excretion rate			
Overnight ($\mu\text{g}/\text{min}$)	<20	20–200	>200
24 Hours (mg/24 hours)	<30	30–300	>300

Box 1: Clinical definition of diabetic nephropathy

- Progressive rise in urine albumin excretion.
- Progressive rise in blood pressure.
- Eventual decline in glomerular filtration rate and end stage renal failure.
- In the presence of diabetic retinopathy.
- Accompanied by progressive rise in cardiovascular risk.

In non-white individuals, the cumulative risk of nephropathy is almost certainly higher and the disease may develop more rapidly than in white people. The most intensively studied population is the Pima Indians, where more than 50% develop proteinuria within 20 years of diabetes.¹⁷ Longitudinal studies suggest that as in type 1 diabetes, glomerular filtration rate is preserved at the microalbuminuric stage. It is particularly concerning that the incidence of end stage renal disease in the Pima Indians continues to rise despite improvements in blood glucose and blood pressure control. In other non-white populations, cross sectional studies indicate a prevalence of microalbuminuria of 30%–60%^{18–21} and longitudinal studies suggest a rate of progression from normal albumin excretion to microalbuminuria of around 4%.²²

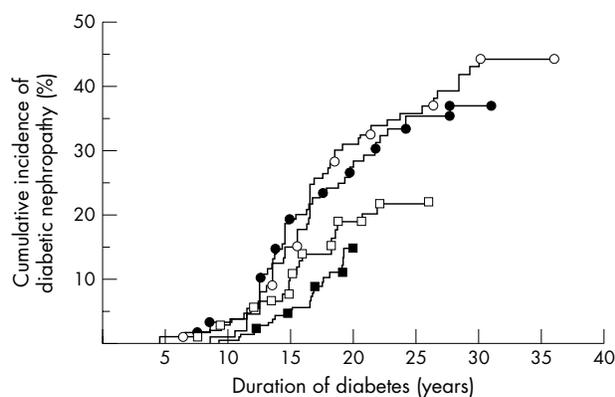


Figure 1 The changing incidence of proteinuria in type 1 diabetes. The cumulative incidence of diabetic nephropathy in 600 type 1 diabetic patients with onset of diabetes from 1965–69 ($n=113$, open circles), 1970–74 ($n=130$, closed circles), 1975–79 ($n=113$, open squares), and 1979–84 ($n=244$, closed squares); $p<0.001$, log rank test, pooled over strata. (Reproduced from Hovind *et al* with permission.)

Box 2: Changing natural history of diabetic nephropathy**Type 1 and white type 2 diabetic patients**

- Microalbuminuria develops at a rate of 2%–3% per annum.
- The cumulative incidence of microalbuminuria is ~50% over a life time of diabetes.
- ~One third of microalbuminuric patients progress to proteinuria.
- Almost all proteinuric patients develop end stage renal disease or die prematurely of cardiovascular disease.
- Long duration patients may not be protected.

Non-white type 2 diabetic patients

- Microalbuminuria develops at a rate of ~4% per annum.
- The cumulative incidence of microalbuminuria is ~50% at 20 years' duration of diabetes.
- Progression from microalbuminuria to proteinuria and end stage renal disease may occur faster than in type 1 diabetes.

End stage renal disease

Worldwide, diabetic nephropathy is now the single commonest cause of entry to renal replacement therapy (RRT) programmes.²³ The incidence of end stage renal disease caused by diabetes was 148 per million population in the United States in 2001, 44.3% of the population beginning RRT having diabetes. However, the proportion of new entrants to RRT with diabetes varies widely geographically, from 54.4% in Brunei to 9.7% in Bulgaria (table 2). In most countries, the proportion of entrants to RRT with diabetes has risen steadily in the last 20 years. However, in the UK, this has not happened.²⁴ In 2001, 18% of new entrants to RRT had diabetes. Methodological differences in data collection undoubtedly account for some of these widely varying figures, but one important factor is the racial mixture of the population: the higher the proportion of individuals from ethnic minorities in the general population, the higher the incidence of diabetes in those entering RRT. For example, in the UK, in the white population entering RRT, 10% had diabetes, while 20% of those from the ethnic minorities beginning RRT had diabetes.

Factors associated with diabetic nephropathy**Cardiovascular disease**

Many studies over the last 10 years have emphasised the close links between diabetic nephropathy and cardiovascular disease (box 3). As albuminuria rises, cardiovascular risk

Table 2 Proportion of individuals beginning renal replacement therapy with diabetes

Country	Proportion with diabetes (%)
Brunei	54
United States	44
Pakistan	40
New Zealand	37
Canada	33
Greece	27
Sweden	26
Denmark	23
Bulgaria	10

Box 3: Cardiovascular risk and diabetic nephropathy

Cardiovascular risk increase as nephropathy progresses. In type 2 diabetes:

- Risk is increased 2–3-fold in microalbuminuric compared with normoalbuminuric patients.
- Risk is increased 10-fold in proteinuric compared with normoalbuminuric patients.
- Average life expectancy on dialysis is two years, main cause of death being cardiovascular.

rises, in both type 1 and type 2 diabetes. In type 1 diabetic patients with microalbuminuria the relative risk of cardiovascular death is 1.2 times that of normoalbuminuric type 1 diabetic patients,^{25–26} and in proteinuria the risk is increased 10-fold.^{27–28} In type 2 diabetes, a meta-analysis suggested a 2–3-fold increase in cardiovascular risk in microalbuminuric compared with normoalbuminuric type 2 diabetic patients,²⁹ and in proteinuric patients the risk is increased 10-fold.³⁰ In the United Kingdom Prospective Diabetes Study (UKPDS), annual rates of death from cardiovascular causes were 0.7% for normoalbuminuric individuals, 2.0% in those with microalbuminuria, 3.5% in proteinuric patients, and 12.1% in those with raised serum creatinine or on RRT.¹⁵ This increasing trend is not explained by the excess of traditional and novel cardiovascular risk factors demonstrated in those with albuminuria but may represent a common, perhaps genetically determined, underlying pathology. Renal disease from non-diabetic causes also increases cardiovascular risk, but the risk is magnified in diabetes.

Other associations

In addition to higher blood pressure, more retinopathy and premature cardiovascular disease, diabetic patients with nephropathy have more neuropathy, more marked dyslipidaemias (particularly low high density lipoprotein-cholesterol and higher triglycerides), poorer glycaemic control, more marked insulin resistance and left ventricular hypertrophy and dysfunction than diabetic individuals with normal albumin excretion. These abnormalities tend to worsen as proteinuria rises. The two factors most important in the initiation and progression of nephropathy are blood glucose and blood pressure. Loss of nocturnal “dipping” of blood pressure, perhaps due to autonomic neuropathy, may be present before daytime blood pressure has risen and may contribute significantly to the early blood pressure load on the kidney. Dyslipidaemia and smoking may also be deleterious, although hard evidence is lacking.

PATHOPHYSIOLOGY OF ALBUMINURIA

Structural abnormalities (box 4)

It is generally believed that the increased urine albumin excretion in diabetic nephropathy is mostly glomerular in origin. For albumin to appear in the urine it must cross the glomerular filtration barrier, which consists of fenestrated glomerular endothelial cells, the glomerular basement membrane, and the glomerular epithelial cell or podocyte (fig 2). It has long been appreciated that increased intraglomerular pressure, loss of negatively charged glycosaminoglycans in the basement membrane and, later in the disease process, increased basement membrane pore size, all contribute to the albuminuria. Well described microscopic abnormalities include thickening of the glomerular basement membrane, accumulation of mesangial matrix, and increased numbers of mesangial cells. As disease advances, there is a

Box 4: Renal structural abnormalities in diabetic nephropathy

Glomerular

- Increased glomerular basement membrane thickness.
- Mesangial expansion (cell number and matrix).
- Podocyte effacement and loss.

Tubulointerstitial

- Increased tubular basement membrane thickness.
- Tubular atrophy.
- Interstitial fibrosis.
- Arteriosclerosis.

close relationship between mesangial expansion and declining glomerular filtration.³¹ Mesangial expansion also correlates inversely with capillary filtration surface area, which itself correlates to glomerular filtration rate.

Changes in the tubulointerstitium, including thickening of the tubular basement membrane, tubular atrophy, interstitial fibrosis and arteriosclerosis, are also well described. Interstitial enlargement correlates with glomerular filtration, albuminuria, and mesangial expansion. It has been suggested that the accumulation of protein in the cytoplasm of proximal tubular cells causes an inflammatory reaction which leads to tubulointerstitial lesions.³²

Recently, it has been demonstrated that the podocyte may also have a role in increasing proteinuria and developing glomerulosclerosis. The podocyte is a terminally differentiated epithelial cell with a cell body from which numerous processes branch.³³ These processes divide successively until the terminal foot process rests on the glomerular basement membrane (fig 2). Foot processes interdigitate so that neighbouring foot processes are from different podocytes. The podocyte, via the foot processes, provides structural support for the glomerular capillaries, buffers intraglomerular pressure, and is the final layer in the barrier to protein passage across the glomerulus into the urinary space. Like the basement membrane, the podocyte is covered by negatively

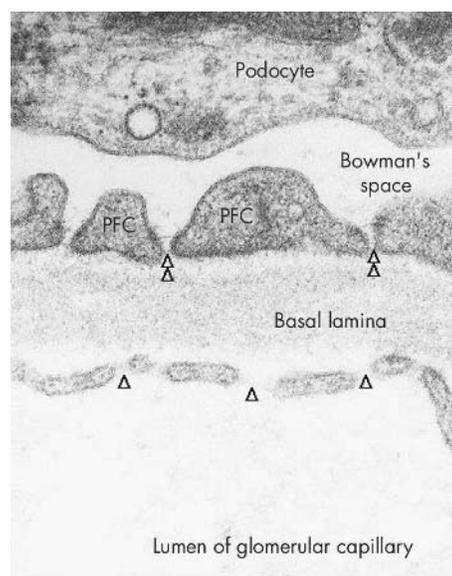


Figure 2 High power electron micrograph showing the glomerular filtration barrier (PFC, podocyte foot process).

charged molecules, which help repel anionic proteins such as albumin. In addition, the negative charge helps maintain open the slit diaphragm, the structure which bridges the gap between adjacent foot processes. The slit diaphragm is essential in preventing proteinuria, slit diaphragm proteins such as nephrin having an essential role in preventing escape of protein into Bowman's space.

In both human and experimental diabetes, podocyte morphology is abnormal.³⁴ The foot processes broaden and efface. Eventually there is loss of the podocyte itself. Podocytes cannot regenerate so this loss cannot be compensated for. There is also decreased expression of nephrin mRNA and protein.³⁵ 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. Whether these are primary abnormalities in the development of proteinuria in diabetes, or occur later in the disease process is a matter of some controversy currently.

Cellular and molecular mechanisms important in the development of nephropathy (box 5)

Abnormalities in many cellular processes have been described in renal cells in experimental and/or human diabetes. Most work so far has focused on the glomerular endothelial and mesangial cells. Direct effects of hyperglycaemia *per se* (glucose toxicity), glycation, and formation of advanced glycation products and increased flux through the polyol and hexosamine pathways have all been implicated in the pathogenesis of diabetic nephropathy. It has recently been suggested that the central abnormality linking all of these pathways is oxidative stress, a defect in the mitochondrial electron transport chain resulting in over-production of reactive oxidative stress molecules which stimulate each of the above pathways.³⁶

Increased activity of a large number of growth factors has been demonstrated in diabetes.³⁷ Transforming growth factor β -1 and connective tissue growth factor may drive the fibrotic changes seen in mesangium and interstitium. Elements of the growth hormone axis, including growth hormone and insulin-like growth factor-1 appear to be associated with glomerular hyperfiltration and hypertrophy. Vascular endothelial growth factor, synthesised by the podocyte, has a major role in maintaining the fenestrae in glomerular endothelial cells. In addition to its pressor effects leading to preferential constriction of the efferent glomerular arteriole, angiotensin II increases glomerular capillary permeability to proteins and its growth effects stimulate mesangial cell proliferation and accumulation of mesangial matrix.

Box 5: Factors involved in the pathophysiology of diabetic nephropathy

- Genetic susceptibility to renal and cardiovascular disease.
- Haemodynamic—raised intraglomerular pressure.
- Biochemical—glucose, protein kinase C, diacyl glycerol, etc.
- Growth factors—for example, insulin-like growth factor-1, transforming growth factor- β , connective tissue growth factor.
- Vasoactive factors—for example, vascular endothelial growth factor, angiotensins, endothelin.

Many of the above growth factors and hormones exert their effects by activating specific intracellular signalling molecules in mesangial, glomerular endothelial, and tubular cells. Glucose itself also stimulates some signalling molecules, as may the raised intraglomerular pressure. Several isoforms of protein kinase C, diacyl glycerol, mitogenic kinases, and transcription factors are all activated in diabetic nephropathy.

Haemodynamic abnormalities

There is a wealth of evidence from experimental diabetic models that intraglomerular pressure is raised, due to relative constriction of the efferent glomerular arteriole.³⁸ The increased pressure is thought to precipitate glomerular damage by direct pressure effects and indirectly by increasing proteinuria. Recently, in elegant experimental studies, it has been demonstrated that stretch of human mesangial cells activates p38 mitogen activated protein kinase via a protein kinase C dependent mechanism, which in turn induces transforming growth factor- β 1 and fibronectin expression.³⁹ Thus raised intraglomerular pressure may also exacerbate cellular and biochemical changes.

Genetic influences

The fact that only a subset of people with diabetes develop nephropathy has long been interpreted as evidence that there is a genetic susceptibility to the development of nephropathy. Twin and family studies in type 1 and type 2 diabetes support this. Many studies have demonstrated an excess of hypertension, dyslipidaemias, insulin resistance, and premature cardiovascular disease in individuals with diabetic nephropathy compared with diabetic individuals with normal albumin excretion. Family studies have also demonstrated an excess of these features in first degree relatives of diabetic nephropathy patients compared with first degree relatives of patients with diabetes but no nephropathy.⁴⁰⁻⁴¹ Thus it may be that the genetic factor in the development of nephropathy also influences the susceptibility to cardiovascular risk factors and premature cardiovascular disease.

Many of the studies searching for a specific gene related to diabetic nephropathy are limited by insufficient power and failure to define carefully enough the control non-nephropathic groups. Thus much of the current literature is contradictory.⁴² The development of DNA repositories from clinically well characterised individuals with and without diabetic nephropathy will undoubtedly help in the future. Interpretation of the data is further complicated by very recent reports that genotype expression varies with the degree of hyperglycaemia and with intraglomerular pressure. Opinion is divided as to whether there is one major gene effect or a number of smaller effects. At the moment, no gene with a large effect has been identified. Small effects of a variety of polymorphisms in various genes have been reported, at least in some studies, for example of the renin-angiotensin pathway, peroxisome proliferator activated receptor gamma, endothelial nitric oxide, glucose transporter 1, aldose reductase, and apolipoprotein E. It has been suggested that individuals with the D allele of the angiotensin converting enzyme (ACE) gene may have faster rate of loss of glomerular function and less response to ACE inhibition.

SCREENING FOR DIABETIC NEPHROPATHY AND MONITORING RENAL FUNCTION

Detection of diabetic nephropathy as early in the disease process as possible currently offers the best chance of delaying or possibly preventing progression to end stage disease. Thus screening for microalbuminuria and proteinuria in a structured, regular manner is recommended.⁴³ Most guidelines suggest annual screening, ideally using an

Box 6: Screening for diabetic nephropathy

- Annual urine test and serum creatinine.
- In stable glucose control.
- No symptoms of urinary tract infection.
- First morning urine sample if possible.
- Sensitive and specific test for urine albumin.
- Repeat positive tests twice within three months.

early morning urine sample to avoid the variable effects of upright posture on albumin excretion. A quantitative, laboratory based, sensitive assay, specific for albumin, is preferable. The albumin:creatinine ratio should be calculated; albumin concentration on its own is unreliable. If the ratio exceeds the upper limit for microalbuminuria (see table 1), then a less sensitive, conventional assay for total protein should be performed.

Screening should be performed under standardised conditions designed to reduce false positive results as much as possible (box 6). Thus screening ideally is performed using an early morning urine sample, when the individual is in stable glucose control, in the absence of intercurrent acute illnesses and in the absence of symptoms of urinary tract infection. Despite these precautions, there remains a huge day-to-day variation in albumin excretion. Hence positive samples should be repeated twice as soon as possible. Urine albumin is stable at room temperature for at least two weeks, so samples from consecutive mornings can be brought to clinic together or even posted to the laboratory. If two out of these three tests are positive, then microalbuminuria or proteinuria is confirmed.

Once persistent microalbuminuria or proteinuria is detected, urine should be tested at each clinic visit, using an early morning urine sample. There is some evidence that in addition to the absolute level of urine albumin excretion, the rate of change of albuminuria over one year independently predicts mortality and cardiovascular events.⁴⁴ There is no need to perform 24 hour urine collections for routine clinical purposes. Serum creatinine should also be measured, although it will remain within the normal range until high microalbuminuria/conventional proteinuria is present. Once the serum creatinine is outwith the normal reference range, progress towards end stage renal disease can be monitored by plotting the reciprocal of the serum creatinine against time—in individual patients, the slope of this plot is linear. Alternatively, glomerular filtration can be estimated by the Cockcroft Gault or Modification of Diet in Renal Disease study equations.

Recently, assays for a naturally occurring substance, cystatin C, which accumulates in blood as glomerular filtration declines, have been developed. Cross sectional studies appear to show that cystatin C rises outwith the reference range before serum creatinine and correlates better with iohexol glomerular filtration rate than creatinine clearance or glomerular filtration rate calculated by the Cockcroft-Gault equation.^{45–46} Cystatin C is assayed by an automated immunoturbidimetric assay, so that it would be applicable to routine clinical practice if longitudinal studies confirm its promise.

The presence of microalbuminuria or proteinuria does not necessarily imply diabetic nephropathy and other causes of renal disease may need to be excluded. A full clinical history and examination for signs of other systemic illness such as autoimmune disease are necessary. In type 1 diabetes, if the person has retinopathy and the progressive rise in

albuminuria, serum creatinine and blood pressure is in keeping with the duration of diabetes and the expected natural history of diabetic nephropathy, no further investigations are required. In type 2 diabetes, the relationship of nephropathy to retinopathy and duration of diabetes are less tight but again, if there are no suspicious features, no further investigation is required. If there is doubt, testing for autoantibodies and renal ultrasound may be helpful: in diabetic nephropathy, the kidneys are symmetrical and of normal size. Renal biopsy is also occasionally required; this procedure is safe when performed under ultrasound guidance using a pre-set biopsy gun.

PRIMARY PREVENTION OF NEPHROPATHY (BOX 7) Blood glucose control

The ultimate aim is to prevent the development of diabetic nephropathy. Both the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes⁴⁷ and the UKPDS in type 2 diabetes⁴⁸ demonstrated that in individuals with normal albumin excretion at outset, the lower the blood glucose level long term, the lower the risk of developing microalbuminuria. In neither study was a threshold of glycated haemoglobin (HbA_{1c}) demonstrated, below which further reduction in risk was not gained.^{49–50} Thus for prevention of nephropathy, the lowest possible HbA_{1c} for the individual patient is the target. Several studies in type 1 diabetes suggest that the effect of tight blood glucose control in delaying the onset of nephropathy may persist for longer than the actual period of tight control. The Epidemiology of Diabetes Interventions and Complications study, the open, non-randomised follow up of the DCCT patients, has now reported eight year data.⁵¹ The proportion of initially normoalbuminuric patients developing microalbuminuria (6.8% v 15.8%), proteinuria (1.4% v 9.4%), hypertension (29.0% v 40.3%), and serum creatinine >176 µmol/l (5% v 19%) were all significantly reduced in patients previously randomised to intensive compared with conventional treatment, despite similar HbA_{1c} levels during open follow up.

Blood pressure control

Good control of systemic blood pressure also reduces the risk of nephropathy. In the UKPDS, the lower the blood pressure, the lower the risk of developing microalbuminuria.⁵² Again, there was no threshold blood pressure below which further reduction did not result in further lowering of risk.⁵³ However, an upper limit of acceptable blood pressure has generally been agreed at 140/80 mm Hg. There is no great evidence to support the use of one particular class of antihypertensive agent over another in the primary prevention of nephropathy: the most important point is to lower the blood pressure. It is noteworthy that blood pressure control seems to be more frequently achieved than glucose control in clinical practice,⁵⁴ and that hypertension control is more cost

Box 7: Primary prevention of nephropathy

- Tight blood glucose control:
 - <7.5% on insulin.
 - <6.5% not on insulin.
- Tight blood pressure control:
 - <140/80 mm Hg for type 2.
- ?Non-smoking.
- ?Statin therapy.

Box 8: Management of microalbuminuria and proteinuria

- Inhibition of renin-angiotensin system.
- Tight blood pressure control:
 - <120/70 mm Hg type 1 diabetes.
 - <130/75 mm Hg type 2 diabetes.
- Moderate protein intake:
 - ~1 g/kg body weight/day.
- ?Tight blood glucose control.
- Statin therapy.
- Aspirin.

effective than glucose control in preventing tissue complications of diabetes.⁵⁵

In type 1 diabetes, there are no data on the effectiveness of lowering blood pressure on the primary prevention of nephropathy; those trials which have been performed have been of insufficient length to allow valid conclusions.

MANAGEMENT OF MICROALBUMINURIA AND PROTEINURIA (BOX 8)

Once urinary albumin excretion is raised, it may not be possible to stop progression of nephropathy completely but it is certainly possible to delay the process substantially. The role of tight glucose control is uncertain, whereas blood pressure control becomes crucial.

Blood glucose control

Studies examining the effect of tight blood glucose control on progression of nephropathy have been too small or too short to demonstrate convincing benefit.^{10–11} However, it is obviously extremely important to maintain good blood glucose control for other reasons.

Reduction of intraglomerular pressure

As described above, raised intraglomerular pressure is the hallmark of diabetic nephropathy and a major factor in its progression. It rises primarily because of angiotensin II constrictor effects on the efferent glomerular arteriole. Thus first line therapy in the secondary prevention of diabetic nephropathy aims to reduce intraglomerular pressure using inhibitors of the renin-angiotensin system.

In young, type 1 diabetic patients with early nephropathy but “normal” blood pressure, numerous studies have demonstrated that prescription of an ACE inhibitor reduced progression to proteinuria compared with placebo. Initial blood pressure was generally <130/80 mm Hg at entry to these studies and around 120/75 mm Hg on treatment. A meta-analysis has confirmed these beneficial effects, demonstrating an average 65% risk reduction in the development of proteinuria and a threefold increase in the likelihood of regression to normal albumin excretion.⁵⁶ Almost all of this effect was independent of changes in systemic blood pressure and thus has been attributed to specific, intraglomerular effects of ACE inhibition. In most of these studies, maximum doses of drug have been used.

In type 2 diabetes, several studies have been reported in microalbuminuric but “normotensive” individuals, generally defined as blood pressure <140/90 mm Hg.^{57–58} Again, these studies show benefit with ACE inhibitors compared with placebo, in terms of reduction in the numbers progressing to proteinuria and in one, stabilisation of serum creatinine over

five years.⁵⁷ This benefit is also at least partly independent of blood pressure lowering.

Several large studies have been performed in hypertensive patients. In type 1 diabetic patients with proteinuria and rising serum creatinine, addition of ACE inhibition compared with placebo to blood pressure control using other classes of antihypertensive therapy, significantly reduced the numbers reaching a combined end point of death, need for dialysis, or doubling of the serum creatinine.⁵⁹ In microalbuminuric⁶⁰ or proteinuric^{61–62} type 2 diabetic patients, prescription of an angiotensin II receptor antagonist (ATIIRB) significantly reduced the rate of progression of nephropathy but had no effect on cardiovascular outcomes. In the diabetes subgroup of the Heart Outcomes Prevention Evaluation study, changes in albumin excretion were difficult to interpret because of methodological problems.⁶³ The apparent significant reduction in macrovascular end points in those patients randomised to ramipril may have been due to a difference in 24 hour blood pressure not reflected in clinic blood pressure measurements.

Thus in type 1 and type 2 diabetic patients with microalbuminuria or proteinuria, prescription of an inhibitor of the renin-angiotensin system, titrated up to the maximum tolerated dose, is the first line in management, regardless of initial blood pressure. There is often concern that patients, particularly those with type 2 diabetes, may have atherosclerotic renovascular disease and that prescription of an ACE inhibitor or ATIIRB may precipitate acute renal failure. There is no reliable screening test for renovascular disease and it is important not to deny patients the potential benefits of renin-angiotensin system inhibition. Thus renin-angiotensin system inhibitors should be tried in all patients, unless in the rare case where there is a definite contraindication. Patients should begin with the smallest dose, which should be titrated up gradually, with serum creatinine and potassium being checked 1–2 weeks after each change in dose. A small (~20%) rise in serum creatinine is common, but this should plateau. If the creatinine rises steadily, the drug should be withdrawn.

Systemic blood pressure control

Numerous studies have demonstrated the importance of reducing systemic blood pressure as well as intraglomerular pressure in delaying the rate of fall of glomerular filtration. It is well accepted that the rate of fall of glomerular filtration rate can be reduced from around 12 ml/min/year to <5 ml/min/year if arterial blood pressure is adequately controlled. With aggressive antihypertensive therapy, it is possible in at least some patients with persistent proteinuria to reduce protein excretion into the microalbuminuric range for several years and to maintain the glomerular filtration rate.⁶⁴ Likewise, in type 1 patients with nephrotic range proteinuria, good blood pressure control can reduce protein excretion to <600 mg/24 hours for at least one year and decrease the rate of fall of the glomerular filtration rate.⁶⁵

Particularly in type 2 diabetes, but also in type 1 patients with more advanced renal disease, systemic blood pressure will be high despite prescription of the maximum tolerated dose of ACE inhibitor or ATIIRB. Addition of other agents to lower blood pressure further is imperative. In general, the number of agents needed increases as nephropathy advances and it is not uncommon for individuals with rising serum creatinine to require four or five different agents. The choice of additional agents is individual, there being no good add-on trials. It is logical to use a diuretic (thiazide or loop) early: patients are often salt overloaded and many of the trials of ACE inhibitors/ATIIRBs included a diuretic in their regimen. Thereafter, the choice rests on the individual's circumstances.

Long acting calcium channel antagonists, β -blockers, α -blockers, and centrally acting agents may all be required.

Dual blockade of the renin-angiotensin system

Several small, short term studies have explored the comparative and additive effects of ACE inhibitors and ATIIRBs in both type 1^{66–68} and type 2 diabetes.^{69–71} All suggest that reduction in systemic blood pressure and albuminuria is similar with the two classes of drug used individually. When ATIIRBs are added to maximum doses of ACE inhibitors, further reductions in albumin excretion and systemic blood pressure are seen, suggesting that the non-ACE pathways of angiotensin II are important in the development of diabetic nephropathy.⁷² It is currently unclear whether both classes of drugs should be commenced together at diagnosis of microalbuminuria or proteinuria or whether one agent should be used initially, with the second being added only if needed to control blood pressure and proteinuria.

Treatment targets

In type 1 diabetes, target blood pressures <120/70 mm Hg are recommended, with <130/75 mm Hg in type 2 diabetes. However, in the belief that the passage of protein through the glomerulus accelerates damage, some authorities advocate adding additional antihypertensive therapy regardless of blood pressure, aiming to reduce albuminuria into the normal range.⁷³

Reduction in protein intake

A reduction in protein intake reduces the rate of progression of proteinuria in type 1 diabetic patients.⁷⁴ In a small randomised study, patients achieved a protein intake of 0.89 g/kg body weight/day on a “low protein diet” compared with 1.02 g/kg/day on the usual diet.⁷⁵ Although the rate of fall of the glomerular filtration rate was similar in the two groups (3.9 ml/min/year), the number of patients reaching the combined end point of end stage renal disease or death was significantly fewer on the low protein diet (10% v 27%; $p = 0.042$). However, there are concerns about malnutrition and difficulties in further restricting an already limited diet. Thus, in general a pragmatic approach is taken and advice given to reduce protein intake from the high levels usual in diabetes to 0.8–1.0 g/kg body weight/day, but not to impose true protein restriction.

The type of protein ingested may also be important, a diet based on vegetable protein reducing albuminuria more than one with animal proteins.

Managing cardiovascular risk

It is extremely important to remember the extremely high cardiovascular risk of diabetic patients with nephropathy. Aggressive cardiovascular risk factor management is vital and will also reduce the risk of progression of renal disease. In a small study, microalbuminuric type 2 diabetic patients were randomised to usual care or intensive care, following an intensive lifestyle and medical intervention regimen according to a target driven protocol.⁷⁶ 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%.

END STAGE RENAL DISEASE

Perhaps the most important point is the need for early referral to a nephrologist, when serum creatinine is in the range 150–200 $\mu\text{mol/l}$. This allows structured physical and

psychological preparation for RRT. There is abundant evidence that those patients who begin dialysis as an emergency do less well than those in whom treatment is planned. Earlier referral may be necessary in particular circumstances for example if the diagnosis is in doubt, or if blood pressure or fluid balance is difficult to control.

Early referral also allows specialist management of renal bone disease and anaemia, with iron and/or erythropoietin as appropriate.⁷⁷

The need for RRT should be discussed with all patients and those who wish it should have access. Younger patients will usually be offered transplantation. In the work-up for transplantation, full cardiovascular assessment is essential, with exercise testing, (stress) echocardiography, and angiography as indicated in individual patient. Coronary angioplasty or even by-pass surgery may be required before transplantation.

NOVEL THERAPIES

A number of novel therapies have been demonstrated to reduce urine albumin excretion and prevent glomerulosclerosis in a variety of animal models of diabetes (box 9). To date, few of these have been tried in clinical practice, generally in small, short term studies. One therapy, already available, is aldosterone blockade. Activation of the renin-angiotensin system stimulates aldosterone secretion, which may subsequently be involved in renal damage. Aldosterone levels may “rebound” during treatment with inhibitors of the renin-angiotensin system. There is also evidence that aldosterone, independently of the renin-angiotensin system, is an important pathogenic factor in progressive renal disease, promoting fibrosis and collagen formation.⁷⁸ In several experimental models, blockade of aldosterone reduces proteinuria. In one small study of type 2 diabetic patients with early nephropathy already taking an ACE inhibitor, addition of spironolactone 25 mg/day resulted in a 40% decrease in urine albumin excretion and a significant reduction in left ventricular mass over 24 weeks.⁷⁹ In a study reported in abstract of hypertensive, microalbuminuric type 2 diabetic patients, the selective aldosterone antagonist eplerenone reduced proteinuria at least as much as ACE inhibition.⁸⁰ Dual blockade resulted in a further reduction in proteinuria.

Thus selective aldosterone blockade as monotherapy or in combination with inhibitors of the renin-angiotensin system is a potentially useful therapy for preventing progression of diabetic nephropathy.

Box 9: Novel therapies for diabetic nephropathy

- Inhibitors of growth factors and vasopeptides:
 - Insulin-like growth factor-1.
 - Growth hormone.
 - Transforming growth factor- β .
 - Vascular endothelial growth factor neutralising antibodies.
 - Endothelin-1 antagonists.
- Biochemical:
 - Protein kinase C inhibitors.
 - Inhibition of formation of advanced glycation end-products (AGE).
 - AGE cross link breakers.
 - Blockade of receptor for AGE.

Key references

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Web links

- www.USRDS.org
- www.renalreg.com
- www.nice.org.uk

CONCLUSIONS

Diabetic nephropathy is currently the single commonest indication for renal replacement therapy worldwide, and in most countries the numbers of patients with diabetes developing end stage renal disease continues to increase. There is good evidence that tight blood glucose and blood pressure control reduce the risk of developing nephropathy. Once urine albumin excretion is increased, reduction of intraglomerular pressure using inhibitors of the renin-angiotensin system and tight control of systemic blood pressure will delay progression to end stage renal disease. Aggressive management of all classical cardiovascular risk factors reduces the rate of progression of renal and cardiovascular disease. Novel therapies are being developed, but the current challenge is to develop ways of better using those that we already know to be effective.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. Diabetic nephropathy:

- (A) Is the commonest single cause of end stage renal disease worldwide
- (B) Accounts for 20% of new entrants to renal replacement therapy in the United States

- (C) Is commoner in white than non-white individuals with type 2 diabetes
- (D) Is associated with an increase in cardiovascular risk
- (E) Develops in a subset of individuals with type 1 diabetes

2. Microalbuminuria

- (A) Can develop at any duration of diabetes
- (B) Progresses to proteinuria in 75% of people with type 1 diabetes
- (C) Is associated with a 2–3-fold increase in cardiovascular risk compared with normal albumin excretion
- (D) Can be reliably detected by conventional urine dipstick testing
- (E) Is extremely variable day-to-day

3. Histological changes seen in diabetic nephropathy include:

- (A) Increased podocyte number
- (B) Thinning of the tubular basement membrane
- (C) Tubulointerstitial fibrosis
- (D) Glomerulosclerosis
- (E) Mesangial expansion

4. Screening for early diabetic nephropathy:

- (A) Should be carried out annually
- (B) Relies on finding a raised serum creatinine
- (C) Requires a 24 hour urine sample
- (D) Requires confirmation of positive tests
- (E) Measurement of total urine protein is acceptable

5. In the primary prevention of nephropathy:

- (A) Reducing HbA_{1c} from 7.0% to 6.0% does not reduce the risk of nephropathy
- (B) ACE inhibitors are the only effective antihypertensive agents
- (C) Genetic screening is mandatory
- (D) Low protein diet is effective
- (E) Two thirds of those who develop microalbuminuria will progress to end stage renal failure

6. In microalbuminuria and proteinuria:

- (A) ACE inhibitors should not be used when serum creatinine is >200 μmol/l
- (B) The reduction in protein excretion when ACE inhibitor and angiotensin II receptor blocker are used in combination is greater than when each agent is used alone
- (C) Statins are contraindicated
- (D) Cardiovascular risk factors are generally abnormal
- (E) Urine albumin excretion is constant day-to-day

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ANSWERS

1. (A) T, (B) F, (C) F, (D) T, (E) T; 2. (A) T, (B) F, (C) T, (D) F, (E) T; 3. (A) T, (B) F, (C) T, (D) T, (E) T; 4. (A) T, (B) F, (C) F, (D) T, (E) F; 5. (A) F, (B) F, (C) F, (D) F, (E) F; 6. (A) F, (B) T, (C) F, (D) T, (E) F.

IMAGES IN MEDICINE

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Calcified splenic artery



Figure 1 Abdominal radiograph of patient.

An 80 year old frail, demented woman was referred to hospital for being generally unwell and with vague lower abdominal discomfort. As a matter of routine, an abdominal film was also taken (fig 1). Interestingly, though the left upper abdomen was not the site of any pain or discomfort, there was a significant finding. There was a circular calcification in the left upper quadrant, along the course of the splenic artery, which is strongly in favour of a splenic artery calcification. This finding is also quite typical of a splenic artery aneurysm¹; this is not just a radiographic diagnosis alone, but requires confirmation with other modalities like Doppler ultrasound and computed tomography.² In this case further aggressive investigations were not done considering her co-morbid conditions.

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