Int J Diabetes & Metabolism (2005) 13: 1-9

Review

Update in Diabetic Nephropathy

Enyioma N Obineche[1] and Abdu Adem[2]

Department of Internal Medicine[1], Department of Pharmacology[2], Faculty of Medicine & Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates

Abstract

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

Key words: *Diabetes, nephropathy, microalbuminuria, proteinuria, cardiovascular risk*

Introduction

The classical definition of diabetic nephropathy is a progressive rise in urine albumin excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually end stage kidney 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. Diabetic nephropathy is now the single commonest cause of end-stage kidney failure worldwide and is acknowledged as an independent risk factor for cardiovascular disease. In many countries, including the Middle East the majority of diabetic patients starting kidney replacement therapy now have type 2 rather than type 1 diabetes. This review will therefore discuss nephropathy in both type 1 and type 2 diabetes.

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

Earlier literature suggested that the cumulative incidence of microalbuminuria after 30 years of type 1 diabetes was approximately 50% and that 30%-40% of patients would 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] However, more recently, work has shown that the appearance of nephropathy may be delayed.[3-5] The cumulative incidence of microalbuminuria and proteinuria in several more recent studies is 35%-40% and 25% respectively after 25-30 years of diabetes. Initially earlier studies suggested that 80% of type 1 diabetic patients with microalbuminuria would progress to proteinuria.[6,7] However, more recent studies suggest that around one third of microalbuminuric patients will revert to normal albumin excretion and only one third will progress to proteinuria.[8–10] 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.[11] Also in this study, 32% of the initially microalbuminuric patients progressed to proteinuria, in contrast to earlier suggestions that microalbuminuria in long-term duration diabetes was a benign condition.[12]

Thus, the classical natural history of the development of nephropathy in type 1 diabetes is undoubtedly being modified. 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

Correspondence to: Prof. Enyioma N Obineche, Department of Internal Medicine, Faculty of Medicine & Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, UAE.Tel: 971 3 7137 420, Fax: 971 3 7672 995, Email: eobineche@uaeu.ac.ae

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, and patients with diabetes of long duration not protected.

Type 2 diabetes

The cumulative incidence of proteinuria in 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.[13,14]

In non-Caucasians, the cumulative risk of nephropathy is almost certainly higher and the disease may develop more rapidly than in Caucasian people. In Pima Indians (the most intensively studied population) more than 50% develop proteinuria within 20 years of diabetes.[15] 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 kidney disease in the Pima Indians continues to rise despite improvements in blood glucose and blood pressure control. In other non-Caucasian populations, cross sectional studies indicate a prevalence of microalbuminuria of 30%–60%[16-18] and longitudinal studies suggest a rate of progression from normal albumin excretion to microalbuminuria of around 4%.[19]

End-stage kidney disease

Worldwide, diabetic nephropathy is now the single commonest cause of entry to kidney replacement therapy (KRT) programmes.[20] In 2001, the incidence of end-stage kidney disease caused by diabetes was 148 per million population in the United States, 44.3% of the population beginning KRT having diabetes. However, the proportion of new entrants to KRT with diabetes varies widely geographically, from 54.4% in Brunei to 9.7% in Bulgaria.

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. Cardiovascular risk rises, risk increasing albuminuria 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,[21,22] and in proteinuria the risk is increased 10-fold.[23,24] A meta-analysis suggested a 2–3-fold increase in cardiovascular risk in microalbuminuric compared with normoalbuminuric type 2 diabetic patients,[25] and 10-fold in proteinuric patients the risk is increased.[26] In the United Kingdom Prospective Diabetes Study (UKPDS), the 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 KRT.[13] 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. Kidney disease from non-diabetic causes also increases cardiovascular risk, but the risk is much worse 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 increases. Two most important factors in the initiation and progression of nephropathy are blood glucose and blood pressure. Dyslipidaemia and smoking may also be deleterious, although there is no hard evidence yet.

Pathophysiology of Albuminuria

Structural abnormalities

There is a general belief that 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 glomerular epithelial cell or podocyte (Fig 1). It has long been appreciated that increased intraglomerular pressure, loss of negatively charged glycosaminoglycans in the basement membrane and, later, increased basement membrane pore size, all contribute to the albuminuria.

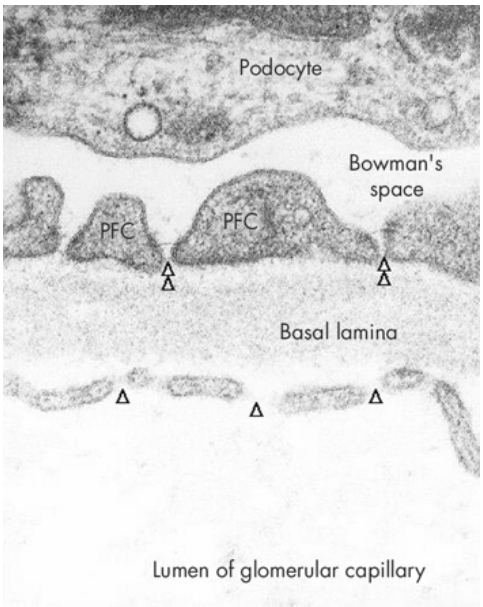

Figure 1: High power electron micrograph showing the glomerular filtration barrier (PFC, podocyte foot process).

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 (µg/min)	<20	20–200	>200
	<30	30–300	>300

Established microscopic abnormalities include thickening of the glomerular basement membrane, accumulation of mesangial matrix, and increase in the numbers of mesangial cells With disease progression there is a close relationship between mesangial expansion and declining glomerular filtration.[27] Mesangial expansion also correlates inversely with capillary filtration surface area, which itself correlates with glomerular filtration rate.

Changes in the tubulointerstitium, including thickening of tubular basement membrane, tubular atrophy, interstitial fibrosis and arteriosclerosis, have been 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.[28]

Recent work has shown that the podocyte may also have a role in increasing proteinuria and development of glomerulosclerosis. The podocyte is a terminally differentiated epithelial cell with a cell body from which numerous processes branch.[29] These processes divide successively until the terminal foot process rests on the glomerular basement membrane. The podocyte, through the foot processes, provides structural support for 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 charged molecules, which help repel anionic proteins such as albumin. The negative charge also helps maintain open the slit diaphragm, the structure which bridges the gap between adjacent foot processes. The slit diaphragm is essential in preventing proteinuria and slit diaphragm proteins like nephrin having an essential role in preventing escape of protein into Bowman's space.

In both human and experimental diabetes, podocyte morphology is abnormal.[30] 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.[31] Abnormalities in several podocyte proteins have been demonstrated to cause proteinuric kidney 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 still conjectural.

Cellular and molecular mechanisms important in the development of nephropathy

Abnormalities in many cellular processes have been described in kidney 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. Recently it has 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.[32]

Increased activity of a large number of growth factors has been demonstrated in diabetes.[33] Transforming growth factor ß-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, plays 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.

Glucose itself also stimulates some signalling molecules, as may the increased intraglomerular pressure. Several isoforms of protein kinase C, diacyl glycerol, mitogenic kinases, and transcription factors are all activated in diabetic nephropathy.

Haemodynamic abnormalities

Evidence from experimental diabetic models indicate that intraglomerular pressure is raised, due to relative constriction of the efferent glomerular arteriole.[34] This increased pressure is thought to precipitate glomerular damage by direct pressure effects and indirectly by increasing proteinuria. Recently, experimental studies have demonstrated that stretching of human mesangial cells activates p38 mitogen activated protein kinase via a protein kinase C dependent mechanism, which in turn induces transforming growth factor-ß1 and fibronectin expression.[35] Therefore, 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.[36,37] It may thus 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 carefully define the control non-nephropathic groups. Thus a lot of current literature is contradictory.[38] 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.

Screening for diabetic nephropathy and monitoring kidney function

Detection of diabetic nephropathy as early as possible in the disease process currently offers the best chance of delaying or possibly preventing progression to end-stage disease. Therefore, screening for microalbuminuria and proteinuria in a structured, regular manner is recommended.[39] Most guidelines suggest annual screening, ideally using an early morning urine sample to avoid 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), 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. 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 symptoms of urinary tract infection. Despite these precautions, there remains a huge day-to-day variation in albumin excretion. Thus positive samples should be repeated as soon as possible. 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. Evidence suggests 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.[40] There is no need to perform 24 hour urine collections for routine clinical purposes. Serum creatinine should also be estimated, although it will remain within the normal range until high microalbuminuria/conventional proteinuria is present. Once the serum creatinine is raised above the normal range, progress towards end stage kidney 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 Kidney 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 above 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.[41,42] 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 kidney 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 there is evidence of retinopathy and 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 kidney ultrasound may be helpful. In diabetic nephropathy, the kidneys are symmetrical and of normal size. Kidney biopsy is also occasionally required. This procedure is safe when performed under ultrasound guidance using a pre-set biopsy gun.

Primary prevention of nephropathy

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 diabetes[43] and the UKPDS in type 2 diabetes[44] demonstrated that in individuals with normal albumin excretion at the outset, the lower the blood glucose level long term, the lower was 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.[45,46] 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.

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 was the risk of developing microalbuminuria.[47] Again, there was no threshold blood pressure below which further reduction did not result in further lowering of risk.[48] However, an upper limit of acceptable blood pressure has generally been agreed at 140/80 mm Hg. There is not much 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,[49] and that hypertension control is more cost effective than glucose control in preventing diabetic complications.[50]

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

Management of Microalbuminuria and Proteinuria

Once urinary albumin excretion is raised, it may not be possible to stop progression of nephropathy completely but it is certainly possible to substantially delay it. The role of tight glucose control is uncertain, whereas blood pressure control is 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.[8,9] However, it is obviously extremely important to maintain good blood glucose control for other reasons.

Reduction of intraglomerular pressure

As already described, 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 the young, type 1 diabetic patients with early nephropathy but "normal" blood pressure, numerous studies have demonstrated that use 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 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.[51] Virtually 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.[52,53] 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.[52] 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.[54] In microalbuminuric[55] or proteinuric[56,57] 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.[58]

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 atheromatous renovascular disease and that prescription of an ACE inhibitor or ATIIRB may precipitate acute kidney 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

Various 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 known 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 some patients with persistent proteinuria to reduce protein excretion into the microalbuminuric range for several years and to maintain the glomerular filtration rate.[59] 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.[60]

Especially in type 2 diabetes, but also in type 1 patients with more advanced kidney 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 is strongly suggested. Generally, the number of agents needed increases as nephropathy advances and it is quite common for individuals with rising serum creatinine to require four or five different agents. 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, ß-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[61–63] and type 2 diabetes.[64,65] 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.[66] 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.

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.[67]

Protein intake

A reduction in protein intake reduces the rate of progression of proteinuria in type 1 diabetic patients.[68] 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.[69] 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 kidney disease or death was significantly fewer on the low protein diet (10% *v* 27%; p = 0.042). However, concerns exist 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.

Cardiovascular risk

It is very important to bear in mind 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 kidney disease. In one 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.[70] 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 Kidney Disease

The most important point is the need for early referral to a nephrologist, when serum creatinine is in the range 150–200 μmol/l. This allows structured physical and psychological preparation for KRT. Abundant evidence exists to the effect that those patients who begin dialysis as an emergency do less well than those in whom treatment is planned. Earlier referral becomes 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 kidney bone disease and anaemia, with iron and/or erythropoietin as appropriate.[71]

The need for KRT 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, 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. A 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 kidney 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 kidney disease,

promoting fibrosis and collagen formation.[72] 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.[73] In another study of hypertensive, microalbuminuric type 2 diabetic patients, the selective aldosterone antagonist eplerenone reduced proteinuria at least as much as ACE inhibition.[74] 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.

Conclusions

Diabetic nephropathy is currently the single commonest indication for kidney replacement therapy worldwide, and in many countries the numbers of patients with diabetes developing end-stage kidney disease continues to increase. Evidence abounds 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 kidney disease. Aggressive management of all classical cardiovascular risk factors reduces the rate of progression of kidney and cardiovascular disease. Novel therapies are being developed, but the current challenge is to develop ways of better applying those that we already know to be effective.

Acknowledgment

We would like to express our sincere appreciation to Ms Reena John for her secretarial assistance.

References

1. Andersen AR, Sandahl Christiansen JK, Andersen K, et al. Diabetic nephropathy in type I (insulin dependent) diabetes: an epidemiological study. Diabetologia 1983; 25:496-501.
2. Borch-Johnsen K, Andersen KP, Deckert T. The effect of proteinuria on relative mortality in type 1 (insulin dependent) diabetes mellitus. Diabetologia 1985; 28:590-596.
3. Harvey JN, Rizvi K, Craney L, et al. Population-based study and analysis of trends in the prevalence of diabetic nephropathy in type 1 diabetes. Diabetic Med 2001; 18:998-1002.
4. Stephensen J, Fuller JH. Microvacsular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia 1994; 37:278-285.
5. Bojestig M, Arnqvist HJ, Hermanssen G, et al. Declining incidence of nephropathy in insulin-dependent diabetes mellitus. N Engl J Med 1994;330:15-18.
6. Kofoed-Enevoldsen A, Borch-Johnsen K, Kriener S, et al. Declining incidence of persistent proteinuria in type I (insulin dependent) diabetic patients in Denmark. Diabetes 1983; 36:205-209.
7. Orchard TJ, Dorman JS, Fraser RE, et al. Prevalence of complications of diabetes in IDDM by sex and duration. Diabetes 1990; 39:1116-1124.
8. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int 1995; 47:1703-1720.
9. Microalbuminruia Collaborative Study Group UK. Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes and microalbuminuria. BMJ 1995; 311:973-977.
10. Perkins B, Ficociello LH, Silva KH, et al. Regression of mciroalbuminruia in type 1 diabetes. N Engl J Med 2003; 348:2285-2293.
11. Arun C, Stiddart J, Mackin P, et al. Significance of microalbuminuria in long-duration type 1 diabetes. Diabetes Care 2003; 26:2144-49.
12. Forsblom CM, Groop PH, Groop LC. Predictive value of microalbuminuria in patients with insulin dependent diabetes of long duration. BMJ 1992; 305:1051-1053.
13. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003; 63:225-232.
14. Gall MA, Hougaard P, Borch-Johnsen K, et al. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin-dependent diabetes mellitus. BMJ 1997; 314:783-788.
15. Nelson RG, Meyer TN, Myers BD, et al. Course of renal disease in Pima Indians with NIDDM. Kidney Int 1997; 52 (suppl 63) :S45-S48.
16. Adedapo KS, Abbiyesuku FM, Adedapo AD, et al. Microalbuminuria in controlled type 2 diabetes mellitus patients. Afr J Med Med Sci 2001; 30:323-326.
17. Vargese A, Deepa R, Rema M, et al. prevalence of microalbuminuria in type 2 diabetes mellitus at a diabetes centre in southern India. Postgrad Med J 2001; 77:399-402.
18. Dasmahapatra A, Bale A, Raghuwanshi MP, et al. Incipient and overt diabetic nephropathy in African Americans with NIDDM. Diabetes Care 1994; 17:297-304.
19. John L, Rao PS, Kanagasabaphy AS. Rate of progression of albuminuria in type II diabetes: five year prospective study from South India. Diabetes Care 1994; 17:888-890.
20. US Renal Data System. USRDS 2003 Annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institute of Health, National

Institute of Diabetes and Digestive and Kidney Disease, 2003.
21. Deckert T, Yokoyama H, Mathiesen E, et al. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. BMJ 1996; 312:871-874.
22. Rossing P, Houggard P, Borch-Johnsen K, et al. Predictors of mortality in IDDM: 10 year observational follow-up study. BMJ 1996; 313:779-784.
23. Borch-Johnsen K, Kreiner S. Protienuria: value as predictor of cardiovascular mortality in insulin-dependent diabetes mellitus. BMJ 1989; 294:1651-1654.
24. Tuomilehto J, Borch-Johnsen K, Molarius A, et al. Incidence of cardiovascular disease in type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy in Finland. Diabetologia 1998; 41:784-790.
25. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systematic overview of the literature. Arch Intern Med 1997; 157:1413-1418.
26. Fuller JH, Stevens LK, Wang SL, et al. Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001; 44 (suppl 2) :S54-S64.
27. Osterby R, Parving HH, Hommel E, et al. Glomerular structure and function in diabetic nephropathy. Diabetes 1990; 39:1057-1063.
28. Gilbert RE, Cooper ME. The tubulo-interstitium in progressive diabetic kidney disease: more than an aftermath of glomerular injury? Kidney Int 1999; 56:1627-1637.
29. Pavenstadt H , Kriz W, Kretzler M. Cell biology of the podocyte. Physiol Rev 2003; 83:253-307.
30. White KE, Bilous RW, Marshall SM, et al. Podocyte number in normotensive type 1 diabetic patients with albuminuria. Diabetes 2002; 51:3083-3089.
31. Langham RG, Kelly DJ, Cox AJ, et al. Proteinuria and the expression of the podocyte slit diaphragm protein nephrin in diabetic nephropathy: effects of angiotensin converting enzyme inhibitors. Diabetologia 2002; 45:1572-1576.
32. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414:813–20.
33. Gnudi L, Gruden G, Viberti GC. Pathogenesis of diabetic neprhopathy. In: Pickup JC, Williams G, eds. Textbook of diabetes. 3rd Ed. Oxford: Blackwell Science Ltd, 2003; 52:1-22.
34. Zatz R, Rentz DB, Mayer TW, et al. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 1986; 77:1925-1930.
35. Gruden G, Zonca S, Hayward A, et al. Mechanical stretch-induced fibronectin and transforming growth factor beta 1 production in human mesangial cells is p38 mitogen-activated protein kinase-dependent. Diabetes 2000; 49:655-661.
36. Earle KS, Walker J, Hill C, et al. Familial clustering of cardiovascular disease in patients with insulin-dependent diabetes and nephropathy. N Engl J Med 1992; 325:673-677.
37. Fogarty DG, Rich SS, Hanna L, et al. Urinary albumin excretion in families with type 2 diabetes is heritable and genetically correlated to blood pressure. Kidney Int 2000; 57:250-257.
38. Merta M, Reiterova J, Rysava R, et al. Genetics of diabetic nephropathy. Nephrol Dial Transplant 2003; 18 (suppl 5): 24-25.
39. National Institute for Clinical Excellence. Management of type 2 diabetes: the prevention and early management of renal disease. London: National Institute for Clinical Excellence, 2002.
40. Yuyun MF, Dinneen SF, Edwards OM, et al. Absolute level and rate of change of albuminuria over 1 year independently predict mortality and cardiovascular events in patients with diabetic nephropathy. Diabetic Med 2003; 20:277-282.
41. Tan GD, Lewis AV, James TJ, et al. Clinical usefulness of cystatin C for the estimation of glomerular filtration rate in type 1 diabetes: reproducibility and accuracy compared with standard measures and iohexol clearance. Diabetes Care 2002; 25:2004-2009.
42. Mussap M, Dalla Vestra M, Fioretto P, et al. Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. Kidney Int 2002; 61:1453-1461.
43. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977-986.
44. UK Prospective Diabetes Study. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352:837-853.
45. Diabetes Control and Complications Trial (DCCT) Research Group. The absence of a glycaemic threshold for the development of long-term complications: the prospective Diabetes Control and Complications Trial. Diabetes 1996; 45:1289-8.
46. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): a prospective observational study. BMJ 2000; 321:405-412.
47. UK Prospective Diabetes Study group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. BMJ 1998; 317:703-713.
48. Adler AL, Stratton IM, Neil NA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321:412-419.

49. Gill GV, Woodward A, Pradhan S, et al. Intensified treatment of type 2 diabetes—positive effects on blood pressure, but not glycaemic control. Q J Med 2003; 96:833-836.
50. CDC Diabetes Cost-Effectiveness Group. Cost-effectiveness of intensive glycaemic control, intensified hypertension control and serum cholesterol level reduction for type 2 diabetes. JAMA 2002; 287:2542-2551.
51. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive ACE inhibitors: a meta-analysis of individual patient data. Ann Intern Med 2001; 144:370-379.
52. Ravid M , Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993; 118:577-581.
53. Sano T, Hotta N, Kawamura T, et al. Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: results of a 4-year prospective, randomised study. Diabetic Med 1996; 13:120-124.
54. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. N Engl J Med 1993; 329:1456-1462.
55. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 2001; 345:870-878.
56. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and nephropathy. N Engl J Med 2001; 345:861-869.
57. Lewis EJ, Hunsucker LG, Clarke WR, et al. Renoprotective effects of the angiotensin II receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345:851–860.
58. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 200; 355:253-259.
59. Hovind P, Rossing P, Tarnow L, et al. Remission and regression in the nephropathy of type 1 diabetes when blood pressure is controlled aggressively. Kidney Int 2001; 60:277-283.
60. Hovind P , Rossing P, Tarnow L, et al. Remission of nephritic-range albuminuria in type 1 diabetic patients. Diabetes Care 2001; 24:1972-1977.
61. Lacourciere Y , Belanger A, Godin C, et al. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. Kidney Int 2000;58:762-769.
62. Jacobsen P, Andersen S, Jensen BR, et al. Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. J Am Soc Nephrol 2003;14:992-999.
63. Jacobsen P, Andersen S, Rossing K, et al. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. Kidney Int 2003;63:1874–1880.
64. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria and non-insulin-dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000;321:1440-1444.
65. Rossing K, Christensen PK, Jensen BR, et al. Dual blockade of the renin-angiotensin system in diabetic nephropathy: a randomised double-blind crossover study. Diabetes Care 2002;25:95-100.
66. Rossing K, Jacobsen P, Pietraszek L, et al. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: a randomised double-blind crossover trial. Diabetes Care 2003;26:2268-2274.
67. Ruggenenti P, Perna A, Remuzzi G, et al. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. Kidney Int 2003;63:2254-2261.
68. Pedrini MT, Levey AS, Lau J, et al. The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal diseases: a meta-analysis. Ann Intern Med 1996;124:627-632.
69. Hansen HP, Tauber-Lassen E, Jensen BR, et al. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int 2002;62:220-228.
70. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348:383-393.
71. Kim DJ, Kim YM, Yun YS, et al. Therapeutic effect of recombinant human erythropoietin on anaemia with erythropoietin deficiency in diabetic patients. Diabetic Med 2003; 20:661-664.
72. Epstein M. Aldosterone receptor blockade and the role of epleronone: evolving prospects. Nephrol Dial Transplant 2003;18:1993-1998.
73. Sato A, Hayashi K, Naruse M, et al. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension 2003;41:64-68.
74. Epstein M, Buckalew V, Martinez F, et al. Antiproteinuric efficacy of epleronone, enalapril and epleronone/enalapril combination in diabetic hypertensives with microalbuminuria. Am J Hypertens 2002;15:24A.