DIABETIC NEPHROPATHY

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SUMMARY

Diabetic nephropathy (DN) is now the commonest cause of end stage renal failure requiring dialysis. There is compelling evidence that glucose control and ACE inhibition may prevent, or at least delay, the onset of DN and progressive renal failure in both Type 1 and Type 2 diabetes. Other factors shown to influence the course of DN include blood pressure control, cigarette smoking and hyperlipidaemia. The latest trials are reviewed and a treatment algorithm suggested.

INTRODUCTION

Diabetes is now the single most common cause of chronic renal failure requiring renal replacement therapy in the developed world. In 1998, 16% of all new cases of chronic renal failure starting dialysis in Scotland were due to diabetes[1] (Figure 1). In the US, diabetes accounts for 42% of new cases, reflecting the higher incidence of diabetes among black and Asian populations.[2]

PATHOPHYSIOLOGY

The sequence of events that leads to end stage renal failure in diabetes has been established. The first discernible abnormality is hyperfiltration which occurs in patients whose albumin excretion rate is still normal. This may progress to microalbuminuria when the urinary albumin excretion rate exceeds 30 mg/24 hours or 20 μg/min. Diabetic nephropathy is then defined by an albumin excretion rate >300 mg/24 hours.

Patients with DN progress at a variable rate towards end stage renal failure. Many mechanisms contribute to the progressive destruction of glomeruli and tubules. These include glomerular hypertrophy, glomerular hypertension and mesangial collagen deposition under the influence of growth factors such as angiotensin II and transforming growth factor $ß_1$ (reviewed by Thomson[3] and Phillips[4]).

EPIDEMIOLOGY

The epidemiology of diabetic renal disease and the progression from normoalbuminuria through microalbuminuria to DN and end stage renal disease have been documented (Figure 2). Twenty-five to 30% of patients with both types of diabetes will develop DN 20 years after diagnosis;[5] this means that a significant percentage of patients do not develop nephropathy despite prolonged hyperglycaemia. In Type 2 diabetes, the risks of macrovascular disease (particularly ischaemic heart disease), peripheral vascular disease and stroke are greater than those of microvascular disease. Nevertheless, more diabetics on renal replacement programmes have Type 2 diabetes than Type 1 diabetes, simply because Type 2 diabetes is more common than Type 1.[6]

GENETIC SUSCEPTIBILITY

Pima Indians have a 50% chance of developing nephropathy after 20 years of diabetes.[7] Higher rates of renal disease are also seen in Indo-Asians in the UK[8] and African-Americans in the US.[6] These data suggest a genetic predisposition to DN. Additional evidence for a genetic link comes from studies that show clustering of nephropathy in families. A study of Pima Indians found that the risk of developing proteinuria in the offspring of diabetic patients increased progressively from 14%, if neither parent had nephropathy, to 23%, if one parent had nephropathy, to 46%, if both

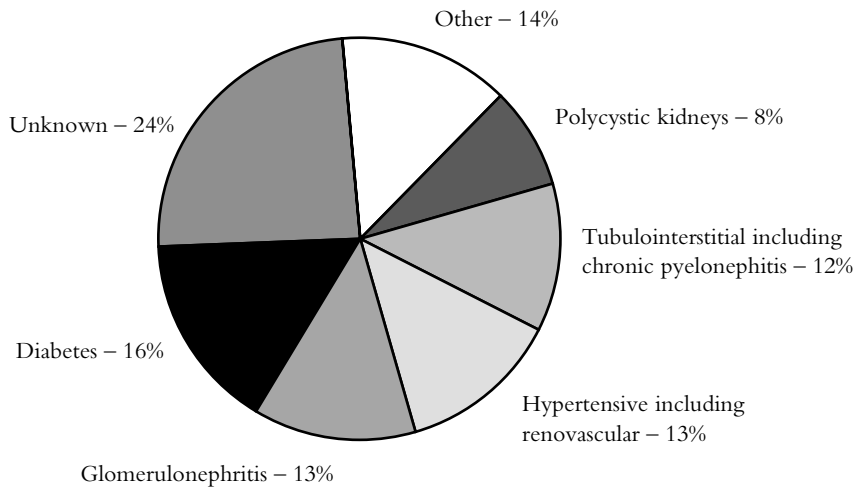

FIGURE 1
Causes of chronic renal failure requiring dialysis in 533 consecutive patients in Scotland 1997–98.[1]

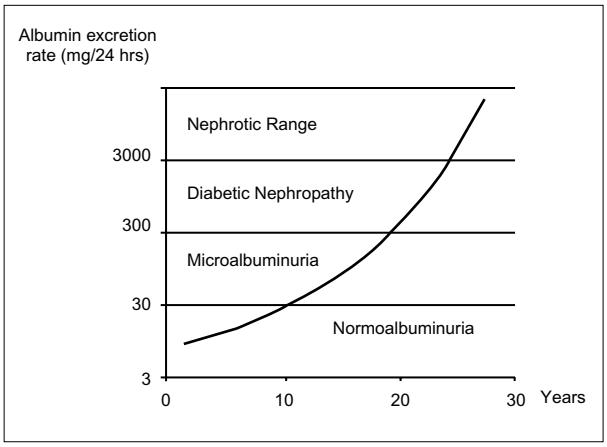

FIGURE 2
Progression of proteinuria in patients with diabetic renal disease who develop nephrotic syndrome, showing the different stages of the disease.

parents had nephropathy.[9] This risk persisted after adjustment for glycaemic control, hypertension and other risk factors. Other studies have confirmed that the risk of nephropathy in siblings is strongly related to the presence of proteinuria in the index case. In one of the largest family studies, the cumulative risk of DN in a sibling was 71·5% if the index case had proteinuria, but only 25·4% if the index case had no proteinuria.[10]

Genetic factors which may be important in the development of DN have been studied using case control and linkage studies. The renin-angiotensin system has been investigated most extensively but the results obtained have been conflicting. A study in 1994 showed that in patients with Type 1 diabetes the presence of a deletion variant of the ACE gene, also shown to correlate with myocardial infarction and stroke, was associated with an odds ratio of 3·88 for developing DN.[11] This deletion variant (D/D genotype) is associated with increased activity of the enzyme and therefore higher angiotensin II levels. However, subsequent studies have reported conflicting results with no association between DN and the D allele.[12] A recent meta-analysis has failed to confirm a link between the D allele and nephropathy in Caucasians although there may be an association in Asian patients.[13]

Some evidence exists to suggest that the ACE D allele may have a role in the progression of nephropathy rather than the susceptibility to nephropathy. Patients with different genotypes respond differently to ACE inhibitors: those with the deletion genotype (D/D) have a smaller reduction in albuminuria after two years of treatment with lisinopril compared to patients with the insertion genotype (I/I) (7·7% vs. 51·3%).[14] Another study confirmed that the rate of decline in renal function was steeper in the group with the D/D genotype compared to the heterozygous genotype (I/D) and I/I genotypes (5·7 ml/min/year vs. 2·6 ml/min/year) in patients with Type 1 diabetes treated with captopril for a median of seven years.[15] Finding genes such as the ACE gene that contribute to nephropathy may enable treatment to be targeted at patients at risk and should lead to the development of new treatment strategies.

CAN DIABETIC NEPHROPATHY BE PREVENTED?

There is compelling evidence that glucose control[16] and ACE inhibition[17] (Figures 3 and 4) may prevent, or at least delay, the onset of DN and progressive renal failure in both Type 1 and Type 2 diabetes. Other factors shown to influence the course of DN include blood pressure control, cigarette smoking and hyperlipidaemia.[18] The evidence on glucose control and ACE inhibition will be reviewed in some detail. Many of the risks for DN are the same as those for diabetic macrovascular disease, but those specific to nephropathy will be discussed later in this paper (see review by Mogensen[19] for more detailed discussion of macrovascular disease).

GLUCOSE CONTROL IN TYPE 1 DIABETES

Tight glucose control is particularly effective in reducing the risk of microvascular disease. The Diabetes Complications and Control Trial (DCCT)[20] examined two groups of Type 1 diabetics: a primary prevention group consisting of 726 patients within five years of diagnosis, with no retinopathy and no microalbuminuria; and a secondary prevention group of 715 patients with diabetes of up to 15 years, all of whom had some retinopathy and 10% of whom had microalbuminuria. Intensive glucose control in both groups (HbA_{1c} 7·2% intensive vs. 9·1% conventional) led to a significant reduction in the progression from normoalbuminuria to microalbuminuria, and microalbuminuria to DN.[20] Only seven patients in DCCT developed proteinuria >300 mg/24 hours with creatinine clearance <70 ml/min which means that this trial was not powered to test the hypothesis that glucose control might slow the progression from diabetic nephropathy to end stage renal disease in Type 1 diabetes. A glycosylated haemoglobin (HbA_{1c}) of <7% can be difficult to achieve in the long-term and to over emphasise it may be profoundly disheartening, especially for people with diabetes. Encouragingly, a follow-up study of patients in DCCT has shown continued benefit four years later, despite a rise in HbA_{1c} from 7 to 7·9%.[21]

GLUCOSE CONTROL IN TYPE 2 DIABETES

The United Kingdom Prospective Diabetes Study (UKPDS) has examined the effect of tight glucose control (sulphonylurea, insulin) versus conventional (diet) control in 3,867 patients with Type 2 diabetes.[22] Glycosylated haemoglobin in the intensive and conventional control groups was 7·0 and 7·9% respectively. Not only did tight glucose control prevent or delay the onset of microalbuminuria in patients whose albumin excretion rate was normal at the start of the trial, but also there was a significant reduction in the number of patients developing DN, and in the number of patients whose creatinine doubled during the nine years of study.

OTHER ASPECTS OF INTENSIVE GLUCOSE CONTROL

The UKPDS, the largest of the trials of intensive glucose control in Type 1 or Type 2 diabetes, failed to show significant reduction in the risk of major cardiovascular events. The other trials were not powered to do so. The trade-off for intensive glucose control in all the trials was hypoglycaemia and weight gain. Encouragingly, intensive treatment in the context of these trials did not impair neuropsychological performance. It was, however, associated with weight gain of approximately 4 kg in patients who were treated intensively with insulin.[16]

ACE INHIBITION IN TYPE 1 DIABETES

The first evidence that ACE inhibitors might have beneficial

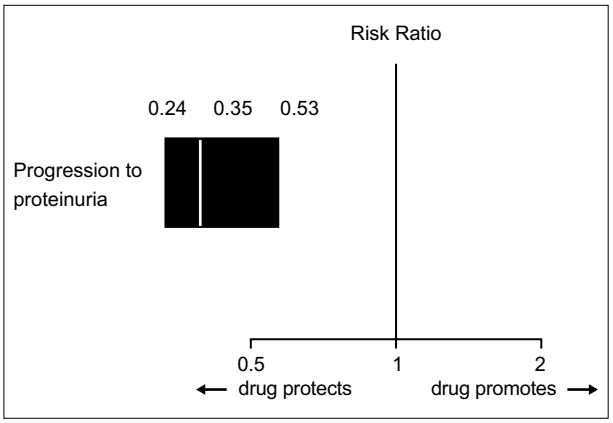

FIGURE 3
Benefit of ACE inhibitors on progression to proteinuria in nine trials of diabetic patients with microalbuminuria.[17]

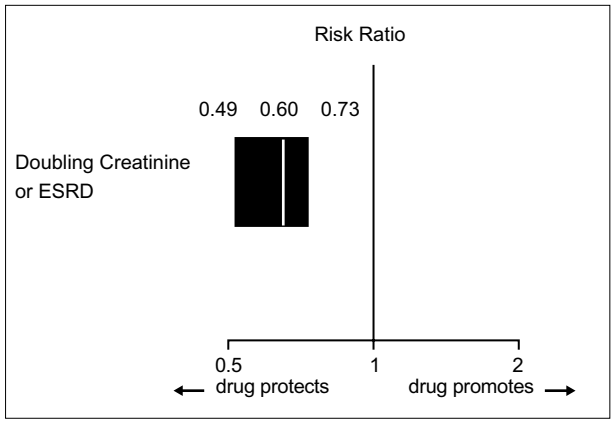

FIGURE 4
Benefit of ACE inhibitors on doubling of serum creatinine or development of end stage renal disease in diabetic and non diabetic subjects with proteinuria and renal insufficiency.[17]

effects on the progression of diabetic renal disease was published in 1986.[23] Numerous studies have followed, and it is now well established that ACE inhibition in Type 1 diabetes can prevent or delay the transition from normotensive microalbuminuria to DN[24] and from DN to end stage renal disease.[25, 26] This evidence even extends to normotensive patients with normoalbuminuria,[27] although the benefits of intervention at this early stage may be less than for intensive glucose control.[20]

ACE INHIBITION IN TYPE 2 DIABETES

Similar benefits from ACE inhibition on the transition from normoalbuminuria to microalbuminuria,[28] and microalbuminuria to DN have also been observed in Type 2 diabetes.[24, 29] In the Heart Outcomes Prevention Evaluation (HOPE) study, the largest and most recent trial, 3,577 subjects with diabetes, 98% of whom were Type 2, were randomised to ramipril 10 mg once daily or placebo. Achieved blood pressure after four years was 140/77 in the ramipril group and 143/77 on placebo, a difference of 3/0 mmHg. The main renal outcome was a 24% reduction in progression to DN with ramipril. Such a result clearly implies a beneficial effect on kidney function or structure above and beyond that expected from blood pressure reduction alone, possibly by haemodynamic effects within the kidney or by inhibition of glomerulosclerosis.[30]

The UKPDS, the other major study of ACE inhibition in Type 2 diabetes, showed no discernible effect of captopril on the rate of progression of diabetic renal disease. A possible explanation is that too few diabetics in the UKPDS had microalbuminuria or proteinuria for the renal benefits of ACE inhibition to be realised.[31, 32] Equally, and possibly for the same reason, it has still to be shown that ACE inhibition slows the transition from DN to end stage renal disease in Type 2 diabetes. Studies of ACE inhibition in non-diabetic nephropathy, particularly the Ramipril Efficacy In Nephropathy (REIN) trials, suggest that benefit is likely, at least for patients whose proteinuria is greater than 1·5 g/24 hours.[33, 34]

POTENTIAL HARM WITH ACE INHIBITION

The most serious adverse effect of ACE inhibition is deterioration of renal function in patients who have unrecognised bilateral renovascular disease. The presence of an afferent arterial stenosis requires the action of intrarenal angiotensin II on the efferent arteriole to maintain glomerular capillary pressure. Inhibition of ACE will cause the glomerular capillary pressure to fall in patients with renovascular disease. The ensuing decline in renal function is usually reversible when the drug is withdrawn.[35] Given the increased risk of macrovascular disease in diabetes it is likely that a proportion of these patients will also have renovascular disease. Recent data confirm that patients with atherosclerotic renovascular disease commonly have proteinuria in the DN range (>300 mg/24 hours) so that the two conditions are often difficult to distinguish on clinical grounds alone.[36]

The trials reviewed here are broadly reassuring. No cases of drug withdrawal due to worsening renal function with ACE inhibition were reported in the studies of Type 1[26, 27] or Type 2 diabetes.[31, 32] Only one case of reversible decline in renal function leading to drug withdrawal was described in the studies of non-diabetic nephropathy.[33, 34] These results are likely to underestimate the risk of ACE inhibitor-induced renal impairment in clinical practice because those at highest risk of bilateral renovascular disease were excluded, i.e. the elderly with widespread atherosclerosis. If doubt exists in an individual case then duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography or conventional renal arteriogram should be considered (reviewed by Safian and Textor[37]).

Alternatively a trial of an ACE inhibitor could be given. In an overview of 12 randomised trials of ACE inhibitors or angiotensin receptor blockers in patients with pre-existing renal insufficiency, Bakris and Weir[38] found that an initial increase in serum creatinine of up to 30% in the first two months was associated with long-term preservation of renal function in patients whose serum creatinine was 125–265 μmol/l initially[38] (Figure 5). Five of the 12 RCTs were in diabetic subjects. In light of their findings, these authors concluded that ACE inhibitors should only be withdrawn in such patients when the rise in creatinine exceeds 30% above baseline within the first two months of treatment, or if hyperkalaemia develops.[38]

OTHER CLASSES OF ANTIHYPERTENSIVE DRUG

Angiotensin receptor blockers have similar antiproteinuric effects as ACE inhibitors[39] though it remains to be

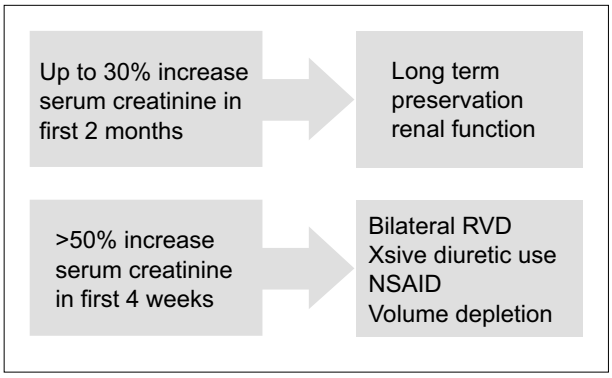

FIGURE 5
Implications of a rise in serum creatinine after an ACE inhibitor in diabetic and non-diabetic subjects with underlying renal disease.

determined whether they can slow the progression of DN. Losartan and irbesartan are currently being evaluated in two major outcome studies; and results presented at the American Society of Hypertension show a reduction in mortality and morbidity.[40, 41] In a study of 199 patients with Type 2 diabetes, blood pressure and urinary albumin excretion were lower on a combination of lisinopril and candesartan than with either drug taken alone.[42] Non-dihydropyridine calcium channel blockers, but not dihydropyridines, also reduce proteinuria in DN, and when given in combination with an ACE inhibitor do so to a greater extent than either agent alone.[43] There remain some unanswered questions about the cardiovascular effects of calcium channel blockers as monotherapy in hypertensive diabetic patients,[44] however, and so for the time being, the drug of choice for prevention of DN remains an ACE inhibitor.

BLOOD PRESSURE CONTROL

The blood pressure goal for patients with diabetes who require antihypertensive drug treatment has recently been revised downwards from 130/85[45] to 130/80,[46] on the grounds that the lower target is associated with the slowest decline in glomerular filtration rate (GFR) and the lowest cardiovascular event rate (Figure 6). The evidence for this comes from two RCTs. Intensively treated patients in the UKPDS had an average blood pressure of 144/82 which was 10/5 mmHg lower than in the control group.[31] Intensively treated diabetic patients in Hypertension Optimal Treatment (HOT) achieved a DBP of 81 mmHg which was 4 mmHg lower than those in the less intensive group.[46]

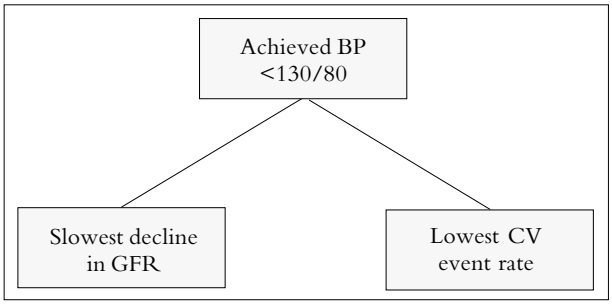

FIGURE 6
The blood pressure goal for patients with diabetes who require antihypertensive drug treatment.

In both studies, intensively treated patients had significantly lower cardiovascular event rates and a greater preservation of renal function.

For some patients an even lower target BP than 130/80 may be desirable. In the Modification of Diet and Renal Disease (MDRD) study, 585 patients with a variety of renal diseases including a small number with Type 2 diabetes who were not taking insulin, whose initial GFR was between 25 and 55 ml/min (equivalent to serum creatinine 150–250 μmol/l), were randomised to intensive or less intensive blood pressure control.[48, 49] The main outcome measure was decline in GFR which was least in those whose achieved Mean Arterial Pressure (MAP) was less than 98 mmHg (equivalent to 130/80). For the subgroups of patients with heavy proteinuria greater than 1 g/24 hours the optimal achieved MAP was less than 92 mmHg (equivalent to 125/75).[49] Such targets are difficult but not impossible to achieve. Success is more likely if clinicians are prepared to prescribe and patients to comply with multiple drug therapy (Table 1).

TABLE 1
Number of antihypertensive drugs to reach target blood pressure in three clinical trials.

Trial	Target BP	Number of drugs
UKPDS	DBP <85	2·7
HOT	DBP <80	3·3
MDRD	MAP <92	3·6

SMOKING AND HYPERLIPIDAEMIA

Cigarette smoking and hyperlipidaemia are important risk factors for coronary heart disease (CHD) generally, and for CHD in patients with diabetes in particular.[50] Both have been shown to contribute to progressive loss of renal function in DN.[51-5] Loss of renal function is slower in ex-smokers[51, 54] and treatment with a statin reduces albumin excretion rate in normotensive diabetics with microalbuminuria.[56] The relations between cigarette smoking, hyperlipidaemia and DN have been reviewed recently.[57, 58]

BENEFITS OF A MULTIFACTORIAL APPROACH

Two studies suggest that a multifactorial approach to DN may yield the greatest benefits. The effects of tight glucose control, ACE inhibition, blood pressure control and protein restriction have recently been evaluated in an uncontrolled study of 13 patients with Type 1 diabetes treated intensively for three years. Glomerular filtration rate rose from 58 to 84 ml/min with a corresponding reduction in albumin excretion from 300 to 92 mg/24 hours during this time.[59] In a larger study of Type 2 diabetes with microalbuminuria, 160 patients were randomised to standard or intensive treatment of blood pressure, glucose and lipids with use of ACE inhibitors unless contraindicated and aspirin for ischaemia, and were followed for four years. Progression to nephropathy was reduced by 73% in the intensively treated group[60] (Figure 7).

CURRENT PRACTICE

A recent audit of 152 patients with diabetes who were

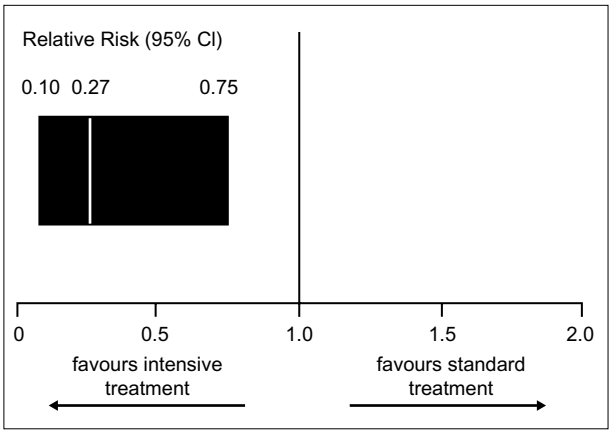

FIGURE 7
Benefits of intensive treatment on relative risk of diabetic nephropathy in the Steno Trial.[60]

referred to a single nephrologist in Bristol has shown that at the time of referral two-thirds of patients had blood pressure >140/90 mmHg, two-thirds of patients had HbA_{1c} >7%, and that two-thirds of those with established vascular disease had total cholesterol >5·5 mmol/l.[61] There were, moreover, disappointingly high numbers of patients who were being treated inappropriately with glibenclamide, metformin or fibrates for the level of their renal function. Nearly half of those with no contraindication to an ACE inhibitor were not receiving this class of drugs. Referral to the nephrologist was considered to be delayed (creatinine >200 μmol/l) in 70% of cases. If data such as these are representative of clinical practice elsewhere then clearly much remains to be done.

CONCLUSIONS

A large body of evidence now supports the view that it is possible to prevent or delay the onset of DN in the majority of patients. A multifactorial strategy incorporating glucose control, ACE inhibition, tight blood pressure control together with advice and intervention on smoking and lipids is likely to be most effective (Figure 8). The challenge for clinicians is to organise the care of patients with diabetic nephropathy so that these targets can be achieved.

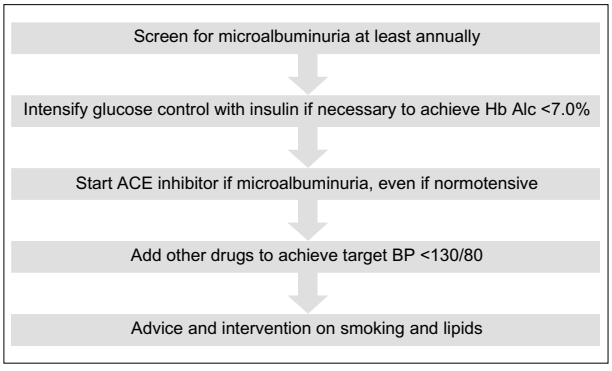

FIGURE 8
Algorithm for prevention of diabetic nephropathy.

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