INTRODUCTION

Diabetic nephropathy, currently the commonest cause of end-stage renal failure in most countries with a Western lifestyle, has reached catastrophic dimensions. In addition to progressing to end-stage renal disease, patients with type 2 diabetes and nephropathy are at especially high risk of cardiovascular death. A multifaceted approach, aiming not only to slow the progression of renal dysfunction but also to reduce the risk of associated complications, particularly cardiovascular disease, is advocated. Current evidence-based guidelines serve a useful adjunctive role in providing target levels for therapeutic intervention.

EARLY IDENTIFICATION AND TREATMENT: MICROALBUMINURIA

Diabetes is unique as a cause of renal dysfunction in that its development may be predicted a decade in advance by the detection of small quantities of urinary albumin termed microalbuminuria. While approximately 80% of patients with type 1 diabetes and microalbuminuria will progress to overt nephropathy over a 10-year period, in the type 2 diabetic patient only 20–50% of patients will progress. However, detection of microalbuminuria in type 2 diabetic patients is not only important for assessing risk of overt nephropathy, but also because of the close association between microalbuminuria and cardiovascular disease, the leading cause of death in these patients.

Annual screening for microalbuminuria should commence at diagnosis in all patients with type 2 diabetes to permit early intervention and to review associated conditions, in particular cardiovascular disease and retinopathy. In the Microvascular Outcomes in People with Diabetes Mellitus Substudy: of the Heart Outcomes Prevention Evaluation (MICRO-HOPE) Study, angiotensin-converting enzyme (ACE) inhibitor treatment provided protection from cardiovascular events and also reduced progression to overt nephropathy in patients with type 2 diabetes and microalbuminuria. Current evidence-based options in patients with type 2 diabetes would therefore include the use of an ACE inhibitor in normotensive microalbuminuric patients to provide cardiovascular protection, and the use of either an ACE inhibitor or angiotensin receptor blocker (ARB) in hypertensive microalbuminuric patients to slow the progression from microalbuminuria to overt nephropathy.

BLOOD PRESSURE

Control of blood pressure (BP) is of paramount importance in slowing the progression of diabetic nephropathy. The US-based Joint National Committee (JNC)-VI guidelines suggest a target blood pressure of <130/85 in...
patients with type 2 diabetes. However, in the presence of nephropathy with >1 g/day proteinuria, a target BP of <125/75 is advocated. Similarly, the US National Kidney Foundation, has suggested that on the basis of recent evidence, a target blood pressure of 130/80 is appropriate.

**CHOICE OF ANTIHYPERTENSIVE DRUG**

Evidence from large, well conducted, double-blind, placebo-controlled, clinical trials has repeatedly shown the efficacy of blockade of the renin-angiotensin-aldosterone system as a key therapeutic strategy in reducing the progression of diabetic nephropathy. In patients with nephropathy and type 1 diabetes, captopril treatment was associated with a 50% reduction in the risk of the combined endpoints of death, dialysis and transplantation that was independent of the small disparity in blood pressure between the groups. In type 2 diabetic patients with nephropathy, two recent trials have shown that the angiotensin II receptor blockers (ARBs) are also effective as renoprotective agents. In the Irbesartan Diabetic Nephropathy Trial (IDNT), 1715 patients were randomized to receive either the ARB, irbesartan, the calcium channel blocker (CCB), amlodipine, or placebo. All patients also received additional conventional antihypertensive medication (non-ACE, non-ARB, non-CCB) as required to control blood pressure. Patients randomized to receive irbesartan were 20% less likely (P=0.02) to reach a composite endpoint of progression of renal disease or death when compared with placebo, and 23% (P=0.006) less likely when compared with amlodipine. Similarly, in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study, 1513 patients with type 2 diabetes and nephropathy were randomized to receive either the ARB, losartan, or placebo, with conventional blood pressure medication (non-ACE, non-ARB) added as necessary to control hypertension. After an average of 3.4 years, patients randomized to receive losartan were 16% less likely (P=0.02) to reach a composite endpoint of doubling of serum creatinine, end-stage renal disease (ESRD) or death. Neither IDNT nor RENAAL included an ACE inhibitor treatment arm. Thus, the relative efficacy of ACE inhibitors and ARBs in type 2 diabetic nephropathy remains unknown.

**Second-line antihypertensive agents**

In clinical practice, achieving recommended blood pressure targets will frequently necessitate the use of multiple antihypertensive drugs, with participants in clinical trials requiring an average of 3.2 different medications. Appropriate adjunctive therapy should be guided by patient considerations but could include β-blockers, CCBs, diuretics and ARBs as these agents have been shown to reduce proteinuria and/or cardiovascular events.

A role for β-blockers in the diabetic patient, particularly those at high cardiovascular risk has emerged following the recent findings of the UK Prospective Diabetes Study (UKPDS) in which both ACE inhibitors and β-blockers were shown to have cardioprotective effects beyond that due to blood pressure reduction alone.

While the use of CCBs in patients with diabetes, particularly the dihydropyridines, has been the subject of controversy, several recent studies indicate that these agents reduce cardiovascular events in the hypertensive diabetic patient. However, when compared directly with ACE inhibitors, as in the Appropriate Blood Pressure Control in Diabetes (ABCD) study and Fosinopril vs. Amlodipine Cardiovascular Events Trial (FACET) Trial, dihydropyridine CCBs provide less cardiovascular protection, although a post hoc analysis of FACET suggested a favourable response to a combination of ACE inhibitor and CCB.

The combination of an ACE inhibitor with an ARB may also be useful in the diabetic patient as suggested in the Candesartan And Lisinopril in Microalbuminuria (CALM) trial, showing an additive effect on blood pressure reduction.

**GLYCAEMIC CONTROL**

There is a clear relationship between glycaemic control and both the development, and the progression of diabetic nephropathy in type 1 and type 2 diabetes. Glycaemic control should be optimized, aiming for a target haemoglobin A1c of 7.0% in most patients. In addition to sulphonylureas, metformin and acarbose, new oral hypoglycaemic agents have recently become available which should assist with attaining good glycaemic control. These agents include the insulin-sensitizing, PPARγ agonist thiazolidendiones (rosiglitazone and pioglitazone) as well as nonsulphonylurea, insulin secretagogues such as repaglinide and neteglinide. Furthermore, the development of insulin analogs with more predictable profiles and the advent of inhaled insulin are likely to make attaining target HbA1c levels easier with improved patient acceptability.

**LIPIDS**

Many patients with type 2 diabetes and nephropathy will have significant coronary artery disease, although this will often be clinically silent. Indeed, most patients with type 2 diabetes and nephropathy will die from cardio-
vascular disease rather than from renal failure per se. Optimization of all cardiovascular risk factors such as dyslipidaemia is therefore an important aspect in the management of patients with diabetic nephropathy. As suggested by the recent consensus conference of the American Heart Association, patients with diabetes should be managed as a coronary disease equivalent with regard to the treatment of risk factors.25 This is especially the case for patients with nephropathy, where an optimal lipid profile should be sought including a suggested target LDL cholesterol of < 2.5 mmol/L.

Furthermore, some pilot experimental and clinical studies have also suggested that the HMGCoA reductase inhibitors may also have favourably influence the course of diabetic nephropathy, independent of their effects on circulating lipoproteins.26

ASPIRIN

The American Diabetes Association (ADA) has recommended that patients with diabetes who are at high risk of cardiovascular disease,27 such as those with nephropathy, should receive prophylactic low-dose aspirin therapy, provided that there are no contraindications such as actively bleeding retinopathy.

SMOKING

Smoking promotes both the onset and progression of diabetic nephropathy as well as providing yet another factor which accelerates cardiovascular disease in patients already at high risk.28

OTHER COMPLICATIONS

Background diabetic retinopathy eventually develops in all patients with diabetes. However, patients with diabetes and nephropathy are at high risk of developing vision threatening retinal complications, clinically significant macular oedema and proliferative diabetic retinopathy.29 Regular ophthalmological assessment is therefore another important aspect of managing the patient with diabetic nephropathy. Similarly, patients with nephropathy are more likely to suffer form neuropathy and peripheral vascular disease such that foot care is an important part in the overall management of the patients with diabetes and renal disease.

CONCLUSION

In conclusion, the treatment of diabetic nephropathy should include a multifaceted approach, aiming not only to slow the progression of renal dysfunction but also to reduce the risk of associated complications, particularly cardiovascular disease. Current evidence-based guidelines serve a useful adjunctive role in providing target levels for therapeutic intervention.

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REFERENCES


