Renal involvement in hypertensive cardiovascular disease

A. M. Sharma

McMaster University, Hamilton, Ontario, Canada

KEYWORDS
Angiotensin II receptor blockers; Nephropathy; Renin–angiotensin–aldosterone system; Renoprotection; Telmisartan

Cardiovascular morbidity and mortality are elevated in renally impaired patients, especially if they are hypertensive. Diabetes is also associated with a high prevalence of cardiovascular morbidity and end-stage renal disease. Albuminuria, elevated serum creatinine, decreased creatinine clearance and proteinuria independently predict cardiovascular risk. Even patients with mild renal impairment should be treated to slow kidney disease progression and reduce vascular damage. Blood pressure control is effective in reducing vascular complications of diabetes, but not all classes of antihypertensive agents provide renoprotection. Angiotensin-converting enzyme inhibitors are superior to beta-blockers in preventing or delaying the loss of kidney function associated with hypertension. The renoprotection appears to be in part independent of the antihypertensive effect. Angiotensin II receptor blockers (ARBs) also reduce the risk of renal complications in diabetics. Telmisartan seems well suited to provide renoprotection because, unlike other ARBs, it is almost exclusively excreted by the liver and no initial dose adjustment is required for patients with mild-to-moderate renal impairment. Other advantages of telmisartan include its very high volume of distribution and long terminal elimination half-life. Clinical trials to evaluate telmisartan will address the problems of diabetes, renal impairment and end-organ disease.

© 2003 The European Society of Cardiology. Published by Elsevier Science Ltd. All rights reserved.

Introduction

End-stage renal disease (ESRD) is a major global public health problem. In the U.S.A. alone there are currently about 300,000 patients with ESRD, and the prevalence is increasing annually at a rate of about 7%. Thus, by the year 2010, in the U.S.A. more than 650,000 patients will be receiving treatment for ESRD. Epidemiological data suggest that the increase in prevalence is seen despite the decline in the prevalence of conventional cardiovascular risk factors, such as hypertension, hypercholesterolaemia and smoking, but parallels an increase in diabetes (Fig. 1).

Indeed, the single most important cause of ESRD in the Western world is diabetic nephropathy. Health statistics clearly point to an epidemic of type 2 diabetes. According to Medicare records of treated ESRD between 1994 and 1996, 41% of the total incidence by primary diagnosis was attributable to diabetes and 28% was ascribed to hypertension, with the remaining 31% due to glomerulonephritis, cystic kidney disease, other urological diseases or other (including unknown)
An ageing population is another important explanation for the increasing prevalence of ESRD. With respect to the two primary causes of ESRD, namely diabetes and hypertension, obesity is thought to be responsible for 85—90% of diabetes cases and 65—75% of hypertension cases. Furthermore, obesity-related glomerulopathy is regarded as an emerging epidemic. Over the period 1986—2000, there has been a 10-fold increase in the incidence of obesity-related glomerulopathy, defined as glomerulomegaly with or without focal segmental glomerulosclerosis.

Prognostic implications of renal disease

The public health problem attributable to diabetic nephropathy is exacerbated because the incidence of cardiovascular morbidity and mortality is very high in patients with ESRD. United States Renal Data System statistics for 1994—1996 show that the incidence of cardiovascular mortality increased linearly in the general population with increasing age, but was uniformly higher, regardless of age, for dialysis patients. In addition, the increase in mortality with age was steeper in dialysis patients. In ESRD patients starting dialysis therapy, survival rates vary depending on the underlying pathology. Those with left ventricular systolic dysfunction generally fared poorly, with few survivors beyond 5 years (Fig. 2). Patients with left ventricular dilatation and concentric left ventricular hypertrophy tended to have a somewhat better survival rate, but the prognosis was likewise poor compared with dialysis patients with no left ventricular disorders. Similarly, patients beginning dialysis therapy had a median survival of only 44 months if they also had ischaemic heart disease, as compared with 56 months if there was no ischaemia. The median times to the onset of heart failure were 24 and 55 months, respectively. The effect of the presence of ischaemia was highly significant ($P=0.0001$).

Microalbuminuria (a proposed marker of generalized vascular damage) is an important predictor of the development of severe nephropathy and cardiovascular mortality in patients with chronic renal failure, cardiovascular disease or diabetes mellitus. Increased serum creatinine ($\geq 140 \mu$mol/l), decreased creatinine clearance and decreased glomerular filtration rate (<44 ml/min) are associated with increased cardiovascular risk. After adjusting for age, sex, glucose tolerance, hypertension, cardiovascular disease and other risk factors, low-density lipoprotein cholesterol, homocysteine, albuminuria, von Willebrand factor, soluble vascular adhesion molecule-1 and C-reactive protein, an inverse association has been identified between renal function and cardiovascular mortality in a general middle-aged to elderly population.

Results of the Systolic hypertension — Europe (Syst-Eur) study likewise indicate that higher levels of serum creatinine and trace or overt proteinuria are associated with an increased number of cardiovascular events and higher mortality in patients aged 60 years or older with isolated systolic hypertension (systolic blood pressure 160—219 mmHg and diastolic blood pressure <95 mmHg). Even when adjusted for age, sex and various other covariates, elevated serum creatinine was associated with a worse prognosis.

There are also data to suggest that the combination of microalbuminuria (30–300 mg
urinary albumin excretion per 24 h) with ST—T segment changes on a resting ECG can identify those at significantly increased risk for all-cause and cardiovascular mortality.\(^\text{15}\) The risk when ST—T segment changes were present in the absence of microalbuminuria was approximately fourfold lower.

In a study of 1906 patients with congestive heart failure, classified as New York Heart Association class III or IV, impaired renal function (as measured by baseline glomerular filtration rate) was a stronger predictor of mortality than was impaired cardiac function (as measured by left ventricular ejection fraction).\(^\text{16}\) The lack of correlation between low baseline glomerular filtration rate and left ventricular ejection fraction suggests that reduced cardiac output is not primarily responsible for impaired renal function.

It must, however, be noted that a recent meta-analysis of longitudinal studies from 1973 to 1999 concluded that moderate renal insufficiency (defined as a serum creatinine concentration of 104—146 µmol/l in women and 122—177 µmol/l in men) was not an independent risk factor for cardiovascular disease in the general population (Fig. 3).\(^\text{17}\) It was, therefore, proposed that correlations found in other studies were likely to be due to co-occurrence of renal insufficiency with traditional cardiovascular risk factors, such as age, hypertension and previous cardiovascular disease. Thus, in a cross-sectional study of 369 patients with chronic renal impairment, patients with even mildly elevated serum creatinine (<186 µmol/l) had, on average, higher serum triglycerides, lower high-density lipoprotein cholesterol and higher serum homocysteine than did age- and sex-matched control individuals with established coronary artery disease but normal creatinine levels.\(^\text{18}\) Also, in the patients with mild renal impairment there was a higher incidence of hypertension and left ventricular hypertrophy.

In a 10-year follow-up study of 503 predominantly non-insulin-dependent diabetic patients, after correction for other independent risk factors (age, serum creatinine level and known duration of microalbuminuria), a urinary albumin concentration greater than 1.5 µmol/l was associated with a hazard ratio of 1.53—2.28 for mortality.\(^\text{19}\) Again, risk factors that significantly correlated with urinary albumin excretion were age (P<0.05), duration of microalbuminuria (P<0.01), systolic blood pressure (P<0.01), serum creatinine (P<0.001) and fasting plasma glucose (P<0.01).

### Role of angiotensin II in renal impairment

Normally functioning kidneys maintain constant intraglomerular pressure by an autoregulatory mechanism that adjusts to variations in mean arterial pressure.\(^\text{20}\) In chronic hypertension with normal renal function, this autoregulation still takes place over the range of more elevated arterial pressures (Fig. 4). By contrast, in chronic hypertension accompanied by chronic renal disease, intraglomerular pressure escapes from autoregulation and increases fairly continuously with arterial pressure. The renin—angiotensin—aldosterone system (RAAS) plays a pivotal role in this regulatory process.\(^\text{21}\)
In diabetic nephropathy, the effects of angiotensin II have been explained by a number of mechanisms. The proposed haemodynamic effects include raising systemic hypertension, eliciting systemic and renal vasoconstriction, causing increased glomerular capillary pressure and permeability, and causing mesangial cell contraction leading to reduction in filtration surface area. Possible non-haemodynamic effects include induction of renal hypertrophy and cell proliferation, stimulation of extracellular matrix synthesis, inhibition of extracellular matrix degradation, stimulation of cytokine production (e.g. tissue growth factor-gamma, vascular endothelial growth factor and endothelin, which all can contribute to end-organ damage) and stimulation of superoxide production. These and other, more general effects of angiotensin II (such as macrophage activation, inflammation and induction of proteinuria) support the peptide’s central role in the pathogenesis of progressive renal injury.

Impact of antihypertensive therapy

A meta-analysis of studies lasting at least 3 years and involving patients with type 2 diabetic nephropathy found that lowering mean arterial blood pressure to levels well below systolic/diastolic blood pressure of 130/85 mmHg was associated with a slower decline in renal function (as measured by glomerular filtration rate). A study of type 2 diabetes, namely the United Kingdom Prospective Diabetes Study (UKPDS), showed that tight control of blood glucose (using either sulphonylureas or insulin to a fasting plasma glucose concentration <6 mmol/l) or of blood pressure (using an angiotensin-converting enzyme [ACE] inhibitor or a beta-blocker) to below 150/85 mmHg independently reduced the risk (by up to 37%) of diabetes-related death, any diabetes-related end-point and all microvascular end-points. Stringent blood pressure control was also associated with a significant reduction (—44%; P=0.013) in stroke incidence. Surprisingly, the risk for macrovascular disease did not change as a result of glucose or blood pressure control, in contrast to the documented reduction in the risk of microvascular complications.

However, another analysis of the UKPDS data showed that, for each 10 mmHg decrease in mean systolic blood pressure, there was an accompanying risk reduction of between 12% and 19% for myocardial infarction, stroke, heart failure, microvascular end-points, lower extremity amputation, any diabetes-related end-point, diabetes-related death and all-cause mortality. An essentially linear relationship was found between systolic blood pressure over the range of 110–170 mmHg and risk reduction for diabetes-related end-points and for diabetes-related and all-cause mortality.

Because of the importance of the RAAS in renal hypertensive disease, its blockade is likely to be an essential component of treatment for patients with impaired renal function. Results from the Heart Outcomes Prevention Evaluation (HOPE) study indicate that the primary trial outcome occurred with a higher incidence (22% vs 15%; P<0.001) in patients with, as compared with those without, mild renal insufficiency quantitated by baseline serum creatinine concentration. This effect was independent of known cardiovascular risks and treatment. The ACE inhibitor ramipril reduced the incidence of the primary end-point of this trial (cardiovascular death, myocardial infarction or stroke) both in patients with and in those without renal insufficiency (hazard ratio 0.8). For all patients, risk increased significantly with increasing serum creatinine concentration (risk ratio 2.34 for a 88.4 µmol/l increase in serum creatinine between quartiles; Fig. 5). In diabetic patients, Microalbuminuria, Cardiovascular and Renal Outcomes in HOPE (MICRO-HOPE) showed that ramipril brought about a risk reduction (relative to placebo) of 24% in total mortality, 37% in cardiovascular death, 22% in myocardial infarction, 33% in stroke, 17% in revascularization and 24% in overt nephropathy (as measured by the urinary albumin/creatinine ratio). The microvascular outcomes (diabetic nephropathy and renal failure) were reduced by ramipril to nearly the same extent as were the cardiovascular outcomes.
Use of angiotensin II receptor blockers in the renally impaired

More complete inhibition of the RAAS may be possible with an angiotensin II receptor blocker (ARB). The ARBs bind specifically to the angiotensin II type 1 (AT₁) receptor, which is believed to play a central role in the pathogenesis of renal disease. As a consequence, angiotensin II, whether formed by the converting enzyme or by other enzymatic pathways, is no longer able to stimulate the AT₁ receptor.

The Irbesartan in Diabetic Nephropathy Trial (IDNT) enrolled 1715 patients with hypertension, type 2 diabetes and proteinuria (900 mg/day). Double-blind treatment consisted of placebo, the calcium channel blocker amlodipine or the ARB irbesartan, with an average follow-up of 2.6 years. Adjunctive antihypertensive therapies (excluding ACE inhibitors, ARBs and calcium channel blockers) could be added to all groups to help achieve blood pressure goals (systolic/diastolic blood pressure 135/85 mmHg). The primary composite end-point of the trial was the time to doubling of serum creatinine, ESRD or death. Irbesartan was significantly superior to placebo, with a relative risk reduction of 20% ($P=0.02$), and to amlodipine, with a relative risk reduction of 23% ($P=0.006$) in prolonging the time to the composite end-point. Serum creatinine increased 24% more slowly in patients treated with irbesartan than in those treated with placebo and 21% more slowly than in the amlodipine group. Irbesartan was also superior to both placebo and amlodipine in reducing the risk of ESRD.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, using the same primary composite end-point of doubling of serum creatinine, ESRD or death as was used in IDNT. It showed that 16% ($P=0.02$) fewer patients treated with the ARB losartan compared with placebo reached one of these end-points during the trial period, which lasted for a mean of 3.4 years.

Telmisartan in management of renal disease

Telmisartan is an ARB that should be particularly appropriate for providing renoprotection. Unlike other ARBS, which are mainly excreted via the kidneys, telmisartan is almost exclusively excreted by the liver. In patients with mild-to-moderate hypertension and moderate renal impairment, telmisartan was shown to be safe and effective in controlling blood pressure without detrimental effects on creatinine clearance. No initial dose adjustment is required for patients with mild-to-moderate renal impairment.

The first evaluation of telmisartan in the management of renal disease in hypertensive patients is the Efficacy and Safety in Patients with Renal Impairment treated with Telmisartan (ESPRIT) study. This multicentre, open-label study, conducted in France, Germany and The Netherlands, was recently completed. It was performed in patients with three strata of stable chronic renal impairment (mild-to-moderate [creatinine clearance 30–74 ml/min per 1.73 m$^3$], severe renal impairment [creatinine clearance <30 ml/min per 1.73 m$^3$] or requiring maintenance haemodialysis) and mild-to-moderate hypertension (seated diastolic blood pressure 90–109 mmHg). The treatment was telmisartan 40 or 80 mg given for 12 weeks and the primary trial end-point was change in blood pressure. The results of this study will be available in 2003.

The Diabetics Exposed to Telmisartan (40/80 mg) And enalaPrIL (10/20 mg) (DETAIL) study is a double-blind, double-dummy, multi-centre study being conducted in Denmark, Finland, The Netherlands, Norway, Sweden and the UK. The 252 patients enrolled in DETAIL met the following criteria: stable serum creatinine for a minimum of 1 year; urinary albumin excretion rate of between 11 and 999 µg/min; and glomerular filtration rate of 70 ml/min per 1.73 m$^3$ or more. The primary outcome of the study will be a change in glomerular filtration rate after 5 years. The planned completion date of the study is 2004.
Conclusion

Current treatment recommendations to slow the progression of kidney disease are based on recognized risk factors, such as high blood pressure, diabetes mellitus, dyslipidaemia, excess dietary protein, smoking and RAAS activity. It is considered advisable to maintain systolic/diastolic blood pressure at below 130/85 mmHg (or below 125/75 mmHg in patients with proteinuria), to maintain tight glucose control in patients with diabetes, to keep the low-density lipoprotein cholesterol levels at less than 100 mg/dl (<2.6 mmol/l), to limit the daily intake of protein to 0.8 g/kg, to abstain from smoking and to provide ACE inhibitor or ARB treatment.38

Numerous studies indicate that impaired renal function is an important predictor of cardiovascular morbidity and mortality. Although tight blood pressure control can reduce the incidence of cardiovascular events in patients with renal disease, it is now evident that blockade of the RAAS is particularly beneficial in further reducing these outcomes and in slowing the progression of renal disease. ACE inhibitors and ARBs will be important tools for combating these entities. The possibility that telmisartan may be a particularly appropriate choice of therapy, based on its unique pharmacological properties, is currently being investigated.

References


