Interventions in chronic renal failure

Treatment may slow progression in some cases

Studies of chronic renal failure in a variety of animal models suggest that once the number of functioning nephrons is reduced to a critical proportion a self perpetuating and progressive deterioration in renal function develops, leading eventually to terminal uraemia. One of the main planks in this explanation is the hyperfiltration hypothesis. This hypothesis postulates that loss of nephrons owing to different causes leads to changes in glomerular haemodynamics in the remaining functioning nephrons with a rise in glomerular capillary pressure (glomerular hypertension) and an increase in filtration rates in the individual nephrons (hyperfiltration). These changes seem to produce increasing proteinuria and progressive glomerulosclerosis culminating in terminal uraemia due to a progressive reduction in the numbers of functioning residual nephrons. It has proved possible in experiments in animals to delay or prevent the development of progressive glomerulosclerosis by ameliorating the haemodynamic changes—either by reducing protein intake or by treatment with angiotensin converting enzyme inhibitors. The converse has also been shown: either a high protein diet or treatment with glucocorticoids increases both the glomerular hypertension and the degree of glomerulosclerosis.

Some observations in these animal models do not, however, support a simple causal relation between the abnormal glomerular haemodynamic changes and progressive glomerulosclerosis. Other mechanisms have been suggested to account for the progressive nature of chronic renal failure. The precipitation-calcification hypothesis postulates that an excess of phosphate causes deposition of calcium phosphate and resultant interstitial and tubular damage. Hyperlipidaemia may be another factor; accumulation of lipid within the mesangial cells may result in the development of focal glomerulosclerosis. Again in animals treatment of hyperlipidaemia has reduced the degree of albuminuria and the incidence of glomerulosclerosis.

It is a big step, however, to attempt to extrapolate the results of the mass of research work in animal models of chronic renal failure (mainly in the rat) to chronic renal failure in humans. Firstly, there is little evidence in humans that reduction of renal mass compromises the function of the remaining nephrons. Long term follow up of donors of kidneys for transplantation has shown only a slightly increased incidence of mild hypertension and proteinuria. In follow up studies of more than 10 years the function of the remaining kidney has not deteriorated. A long term follow up of 32 patients for a mean of 23 years after unilateral nephrectomy in childhood (for various reasons) showed no evidence of an increased incidence of renal impairment or hypertension.

Clinical studies have confirmed that not all patients with chronic renal failure progress inexorably towards terminal uraemia. In a recent study progression of chronic renal failure was analysed in 108 patients by plotting the slope of the reciprocal of the plasma creatinine concentration against time. Seventy patients showed a pattern of linear deterioration and 15 showed non-linear deterioration. In 23 patients, however, the chronic renal failure was stable. Progressive renal failure was usual in patients with chronic glomerulonephritis, diabetic nephropathy, reflux nephropathy, and polycystic kidney disease. By contrast, most of the patients with hypertensive nephrosclerosis, anaeglic nephropathy, and renal impairment after acute renal failure were stable. Among patients with linear deterioration the rate was faster in those with chronic glomerulonephritis and diabetic nephropathy than in those with reflux nephropathy and polycystic kidney disease. The underlying renal disease seems, therefore, to be important in determining progression of chronic renal failure and also the rate at which this deterioration occurs. Clearly clinicians need accurate methods of measuring renal function in order to determine whether chronic renal failure is stable or is progressively deteriorating. Plots of the reciprocal of the serum creatinine concentration against time have frequently been used for this purpose. However, the validity of this method has been seriously questioned, as has the use of measurement of creatinine clearance. Isotopic methods of determining the glomerular filtration rate are to be preferred.

Deterioration in chronic renal failure may be due to continuing activity of the underlying renal disease—as in systemic lupus erythematosus. Several other factors that may result in acute deterioration in chronic renal failure need to be sought and excluded. Their prompt identification and correction may enable renal function to improve and even stabilise at the previous level. These factors include acute sodium and water depletion due to vomiting or diarrhoea, or
both; urinary tract infections; nephrotic drugs including tetracycline, non-steroidal anti-inflammatory drugs and aminoglycosides; and obstruction—for example, prostatic obstruction in elderly men, renal calculus disease, and papillary necrosis in patients with analgesic nephropathy.

One of the most easily observed complications of this disease is the progression of chronic renal failure that occurs in many patients. One approach has been the use of low protein diets. These have been part of the treatment of symptoms of uraemia in patients with severe chronic renal failure for many years, but only relatively recently have they been used at an earlier stage to try to halt or slow down the progression of the disease. Clinical trials have suggested that dietary restriction of protein and phosphorus may be effective in these circumstances. Many of these trials, however, have been criticised on the grounds of poor experimental design. The observation that more frequent clinical follow up (and presumably better control of blood pressure) retards the progression of chronic renal failure has important implications for the design of prospective randomised studies. So far only two prospective, randomised, controlled trials have been reported of low protein diets in patients with chronic renal failure. Rosman et al studied 228 patients and followed 149 for at least 18 months. Those with initial creatinine clearances of 10-30 ml/min/1.73 m² were studied on a protein intake of 0.4 g protein/kg body weight a day while those with creatinine clearances of 31-60 ml/min/1.73 m² received 0.6 g protein/kg/body weight a day. This trial has been criticised because of the use of plots of the reciprocal of serum creatinine concentrations against time to assess the progression of renal failure. Nevertheless, regression analysis indicated that the rate of progression was three to five times slower in patients whose protein was restricted than in controls.

Ihle et al recently reported a prospective, randomised study of a low protein diet (0.4 g protein/kg body weight a day) in 64 patients with initial serum creatinine concentrations ranging from 350-1000 mmol/l. The study was for 18 months. End stage renal failure developed in nine of the 33 patients who were on their normal diet (27%) as compared with two of the 31 patients (6%) who were on the low protein diet. The mean glomerular filtration rate (measured isotopeically) fell substantially in the control group but only very little in the group on the low protein diet. Protein state was checked during the study to see if there was any evidence of protein malnutrition. Serum albumin concentrations did not change, and there were no changes in certain anthropomorphic measurements. A note of caution was sounded, however, because total lymphocyte counts and serum transferrin concentrations both fell. No patient had an opportunistic infection.

A large multicentre cooperative study to define the influence of dietary restriction of protein and phosphorus and also blood pressure control on the progression of chronic renal disease is in progress. Low protein diets are also low in phosphorus. The relative importance of these two variables is not clear. One other aspect of low protein diets is the possible effect of the underlying renal disease and the hemodynamic response to the diet. El Nahas et al have reported maximal benefit in non-glomerular disorders and also that patients with a reactive renal vascular bed improved with a low protein diet while those with a fixed renal plasma flow progressed relentlessly.

**Control of hypertension**

Another important topic is the control of hypertension. Control of accelerated or malignant hypertension is known to be vital to patient survival. Such treatment is indicated whatever the level of renal function at presentation; deterioration of renal function does not necessarily occur. In those patients with severe impairment of renal function on presentation a period of dialysis may be necessary while the blood pressure is controlled. In some patients dialysis may be discontinued later—presumably the renal histopathological lesions of accelerated hypertension regress—but in others the renal failure will not improve and permanent dialysis or renal transplantation will be necessary.

The importance of less severe grades of hypertension in the progression of chronic renal failure, however, is not so easily shown. The kidney lesion may cause hypertension but the kidney may also suffer the effects of hypertension, which are termed nephrosclerosis. The mechanism of hypertensive nephrosclerosis is not clear. One explanation is that thickening of the arteriolar walls with narrowing of the arteriolar lumen results in ischaemia of the glomerulus and glomerulosclerosis. Another explanation is that hypertension may damage the glomeruli more directly by increasing glomerular capillary pressure, which in turn results in glomerulosclerosis.

Careful documentation of the effects of control of blood pressure on the progression of chronic renal failure in humans is limited. In one retrospective study there were no differences between patients who had developed significant loss of renal function and those who did not with respect to duration of hypertension, blood pressure during treatment, antihypertensive regimens, duration of follow up, or initial concentrations of serum creatinine. There was, however, an association between loss of renal function and race, with renal function decreasing in 23% of black patients but in only 11% of white patients. One explanation for these results is that the target level of good blood pressure control (<140/90 mm Hg) needs lowering and may represent in fact inadequate control, particularly in black patients. Whether a further lowering of blood pressure could be achieved without unacceptable side effects remains to be determined.

Another important aspect is the type of antihypertensive agent used to control the blood pressure. The introduction of angiotensin converting enzyme inhibitors has posed several important questions. These agents affect glomerular haemodynamics with preferential vasodilatation of the efferent arterioles. They would therefore be expected to reduce glomerular hypertension, and there is experimental evidence that they do this in animals with chronic renal failure. There is also evidence of beneficial effects on progression of chronic renal failure both in animals and in humans irrespective of blood pressure control. Angiotensin converting enzyme inhibitors may prove to be of value in progressive chronic renal failure not only as antihypertensive agents but also in the absence of hypertension. Prospective, randomised trials using...
the inhibitors are currently in progress.**13** Smith **et al** in a short term study of the effect of captopril on renal haemodynamics in chronic renal failure, however, concluded that the renal microvasculature in stable chronic renal failure was unresponsive to this inhibitor.**13** These authors found no alteration in baseline glomerular filtration rate, effective renal plasma flow, or creatinine clearance with or without captopril.

With the increasing use of angiotensin converting enzyme inhibitors in the treatment of hypertension and perhaps also chronic renal failure and diabetic nephropathy clinicians need to remember the possible side effects. Acute deterioration in renal function may occur in patients with bilateral renal artery stenosis or renal artery stenosis of a solitary kidney.**39 40** This complication is likely to be seen more commonly in elderly patients, with their relatively high incidence of atherosclerosis and renovascular disease. The effect of angiotensin converting enzyme inhibitors on renal haemodynamics has been used as a test to detect renal artery stenosis.**41**

Calcium channel blocking agents have also been shown to protect against progression of chronic renal failure in animals.**42** Whether these and angiotensin converting enzyme inhibitors have any advantage over more conventional antihypertensive agents remains to be determined.

The hyperfiltration hypothesis may also be relevant in diabetes.**43** Current approaches to the prevention and treatment of diabetic nephropathy have been reviewed by Mogensen.**44** The three main lines include better metabolic control, effective antihypertensive treatment, and the use of moderately low protein diets. Patients with borderline hypertension— that is, a blood pressure of 140/90 mm Hg— should probably be treated with a lower target blood pressure of perhaps 135/85 mm Hg. Several accounts of the use of angiotensin converting enzyme inhibitors in diabetic nephropathy have reported improvement in microalbuminuria in incipient diabetic nephropathy and reduction in albuminuria in established diabetic nephropathy.**45 46** Microalbuminuria was also reduced in patients with incipient diabetic nephropathy, however, by conventional antihypertensive treatment.**47** Some long term large scale double blind randomised trials of the inhibitors in patients with incipient diabetic nephropathy are in progress.

Many questions regarding the progression of chronic renal failure remain unanswered. There are several other factors that may be important but require further research. These include the possible contributions of lead,**48** hyperuricaemia;**49** secondary oxalosis,**50** and atrial natriuretic peptide.**51**

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